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Acid-suppressive medications and risk of oesophageal adenocarcinoma in patients with Barrett's oesophagus: a systematic review and meta-analysis

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Abstract

Background and aims—Acid-suppressive medications, particularly proton pump inhibitors (PPIs), may decrease the risk of oesophageal adenocarcinoma (OAC) in patients with Barrett's oesophagus (BO). We performed a systematic review with meta-analysis of studies evaluating the association between acid-suppressive medications (PPIs and histamine receptor antagonists (H2RAs)) and risk of OAC or high-grade dysplasia (BO-HGD) in patients with BO.

Methods—We performed a systematic search of multiple electronic databases and conference proceedings up to June 2013 to identify studies reporting the association between use of acid-suppressive medications and risk of OAC and/or BO-HGD in patients with BO. Summary ORs with 95% CIs were estimated.

Results—We identified seven observational studies (2813 patients with BO, 317 cases of OAC or BO-HGD, 84.4% PPI users). On meta-analysis, PPI use was associated with a 71% reduction in risk of OAC and/or BO-HGD in patients with BO (adjusted OR 0.29; 95% CI 0.12 to 0.79). There was a trend towards a dose–response relationship with PPI use for >2–3 years protective against OAC or BO-HGD (three studies; PPI use >2–3 years vs <2–3 years: OR 0.45 (95% CI 0.19 to 1.06) vs 1.09 (0.47 to 2.56)). Considerable heterogeneity was observed. Two studies reported the

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association between H2RA use and risk of OAC and/or BO-HGD (1352 patients with BO, 156 cases of OAC, 25.4% on H2RAs), and both studies did not show a significant effect.

Conclusions—Based on meta-analysis of observational studies, the use of PPIs is associated with a decreased risk of OAC and/or BO-HGD in patients with BO. None of the studies showed an increased risk of OAC. PPI use should be considered in BO, and chemopreventive trials of PPIs in patients with BO are warranted.

INTRODUCTION

The incidence of oesophageal adenocarcinoma (OAC) has increased more than sixfold in the last three decades in the USA.[1] Barrett's oesophagus (BO) is precursor lesion for OAC and confers a 30–125-fold higher risk of OAC. However, only a small proportion of patients have BO that progresses to OAC. Routine endoscopic surveillance of patients with BO and endoscopic eradication therapy for a subset of patients with high-grade dysplasia (BO-HGD) is recommended.[2] However, this strategy is expensive and limited by suboptimal adherence and access. Hence, there is a great interest in identifying relatively inexpensive and effective chemopreventive strategies for patients with BO.[3–5]

Acid-suppressive medications such as proton pump inhibitors (PPIs) and histamine receptor antagonists (H2RAs) are the most commonly used medications in the management of gastroesophageal reflux disease (GERD). Preclinical studies and early phase biomarker-based chemoprevention trials have shown that PPIs may prevent or delay progression of dysplasia in BO.[67] However, PPI-related acid suppression induced hypergastrinemia and consequent proliferation have led to concerns about oncogenic potential of long-term PPI therapy.[8] Epidemiological studies of the association between acid-suppressive therapy and OAC risk have been conflicting. A large population-based nested case–control study from the UK reported an increased risk of OAC in patients on long-term acid-suppressive therapy, but not independent of underlying GERD symptoms (which prompted acid-suppressive therapy).[9] In contrast, several small observational studies have reported a protective association between PPI therapy and risk of progression to OAC and/or BO-HGD in a cohort of patients with BO.[1011] However, these studies have been limited by the small number of events, precluding a robust estimation of the true association between acid-suppressive medications and risk of OAC.

To better understand this issue, we performed a systematic review with meta-analysis of all studies that investigated the association between acid-suppressive medications, PPIs and H2RAs, and OAC and/or BO-HGD in patients with BO.

METHODS

This systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12] The process followed a priori established protocol.

Selection criteria

We included randomised controlled trials (RCTs) or observational studies (cohort and case–control design) that met the following inclusion criteria: evaluated and clearly defined exposure to PPIs or H2RAs (exposed and unexposed group); reported OAC and/or BO-HGD risk in patients with established BO; and reported HR, relative risk (RR) or OR, or provided data for their calculation. Inclusion was not otherwise restricted by study size, language or publication type. We excluded cross-sectional studies, studies performed in the general population without knowledge of BO status, studies with insufficient information on histological progression to OAC or BO-HGD, and studies comparing medical and surgical therapy for GERD or BO. When there were multiple publications from the same population, we only included data from the most recent comprehensive report.

Data sources and search strategy

First, we conducted a systematic literature search of Medline, Embase, Web of Science and Scopus, from inception through 15 June 2013, with the help of an expert medical librarian, to identify all relevant articles on the association between acid-suppressive medication and risk of OAC in patients with BO. Details of the search strategy are available in the online supplementary appendix. Briefly, a combination of keywords and medical subject heading terms were used, including ‘proton pump inhibitor*’, ‘PPI’, ‘acid suppress*’, ‘omeprazole’, ‘panto-prazole’, ‘esomeprazole’, ‘lansoprazole’, ‘dexlansoprazole’, ‘histamine receptor antagonists’, ‘histamine receptor blockers’, ‘ranitidine’, ‘cimetidine’ AND ‘barrett’s’ OR ‘oesophageal’ AND ‘neoplasia’, ‘oesophageal adenocarcinoma’. Subsequently, two authors independently reviewed the title and abstract of studies identified in the search to exclude studies that did not answer the research question of interest, based on prespecified inclusion and exclusion criteria. The full text of the remaining articles was again independently reviewed to determine whether it contained relevant information. Next, we manually searched the bibliographies of the selected articles and review articles on the topic for additional articles. Third, we performed a manual search of conference proceedings from major gastroenterology meetings (Digestive Diseases Week, United European Gastroenterology Week and Annual Meeting of the American College of Gastroenterology; from 2008 to 2012) for additional abstracts on the topic.

Data abstraction and quality assessment

After study identification, data on study and patient characteristics, exposure and outcome assessment, potential confounding variables and estimates of association were independently abstracted onto a standardised form by two authors. Details of data abstraction are reported in the online supplementary appendix. To estimate the duration–response relationship, using non-users as reference, we measured the association between patients exposed to acid-suppressive medication for a short period of time (<2–3 years) and non-use, and the association between long duration of medication use (>2–3 years) and non-use. Conflicts in data abstraction were resolved by consensus, referring back to the original article. The methodological quality of case–control and cohort studies was assessed by two authors independently (SS and SK) using the Newcastle–Ottawa scale.[13] Any discrepancies were addressed by a joint re-evaluation of the original article.

Outcomes assessed

The primary analysis focused on assessing the risk of progression to OAC and/or BO-HGD in patients with BO, among PPI users (and H2RA users) compared with non-users. We also analysed the time to progression to any neoplasia (OAC or BO-HGD or Barrett's oesophagus with low-grade dysplasia (BO-LGD)) in patients with non-dysplastic BO (time-to-event analysis) based on PPI use, as reported in cohort studies.

We performed pre-planned subgroup analysis based on study design (cohort vs case–control), study location (USA vs non-USA), method of exposure ascertainment (pharmacy prescription database vs self-report vs medical record review) and proportion of patients exposed to medication in entire BO cohort at time of enrolment (>90% vs <90%). To assess the presence of a reflux-independent association between acid-suppressive medication use and risk of progression to OAC and/or BO-HGD, we performed sensitivity analysis restricting analysis to studies which adjusted for the presence of erosive esophagitis or reflux symptoms; likewise, to assess the presence of an independent chemopreventive association, we restricted analysis to studies which adjusted for concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs)/aspirin or statins.

Statistical analysis

We used the random-effects model described by DerSimonian and Laird to calculate summary ORs and 95% CIs.[14] Since outcomes were relatively rare, ORs were considered approximations of RRs or HRs. Maximally adjusted OR, when reported in studies, was used for analysis to account for confounding variables. To estimate what proportion of total variation across studies was due to heterogeneity rather than chance, I^2 statistic was calculated. In this, values of <30%, 30–60%, 60–75% and >75% were suggestive of low, moderate, substantial and considerable heterogeneity, respectively.[15,16] Once heterogeneity was noted, between-study sources of heterogeneity were investigated using subgroup analyses by stratifying original estimates according to study characteristics (as described above). In this analysis also, a p value for differences between subgroups of <0.10 was considered statistically significant. Given the small number of studies identified in our analysis, statistical tests for assessing publications bias were not performed.[17] All p values were two tailed. For all tests (except for heterogeneity), a probability level <0.05 was considered statistically significant. All calculations and graphs were performed using Comprehensive Meta-Analysis (CMA) V.2 (Biostat, Englewood, New Jersey, USA).

RESULTS

From 824 unique studies identified using our search strategy, seven studies (five cohort, two case–control studies) reporting on the association between PPIs and risk of OAC and/or BO-HGD,[10,11,18–22] and two studies (one cohort and one case–control) reporting on the association between H2RAs and relevant outcomes were included.[10,20] The flow diagram summarising study identification and selection is shown in figure 1. There were no RCTs comparing effect of acid-suppressive medications (with no acid-suppressive medications) addressing this question. Four studies were from two overlapping populations,[10,11,23,24] and

hence, only two of the more comprehensive studies were included.[1011] In three studies, there was insufficient information to calculate a measure of association.[25–27]

Characteristics of included studies

Seven studies reported on 2813 patients with non-dysplastic BO (or BO-LGD), of whom 317 progressed to OAC and/or BO-HGD; 84.4% of patients in these studies were PPI users.[101118–22] Table 1 shows the baseline characteristics of the studies. Four of these studies were conducted in the USA, two studies were conducted in Europe and one in Australia. Only one of the US studies was population based at low risk for selection bias[22] and two Dutch studies were multicentred, conducted in a mix of academic and private practices[1018]; three of the American studies were conducted in the military veteran population.[112021] A majority of these patients had non-dysplastic BO (88.5% of patients in cohort studies); one nested case–control study from the national Veteran Affairs cohort did not report baseline dysplasia status of patients with BO.[20] Systematic information on surveillance of BO was provided in only two studies.[1019] Three studies used record linkage with the pharmacy prescription database for exposure assessment[101120]; three studies relied on medical record review[192122] and one on patient self-report.[18]

Four cohort studies reported the risk of progression to advanced neoplasia (OAC or BO-HGD)[10111922] (with no information on risk of progression to OAC or BO-HGD separately), and one study reported the risk of progression to any grade of neoplasia (OAC or BO-HGD or BO-LGD).[21] Two case–control studies included only patients with OAC as cases.[1820] The primary outcome was OAC in 39 and BO-HGD in 69 patients, from 1589 patients. One of the studies by Nguyen *et al*[20] was a nested case–control study within a cohort of patients with BO, and risk estimate was reported as incidence density ratio.

Table 2 shows the baseline characteristics of the patients included in these studies. The mean age at BO diagnosis ranged from 58 to 63 years in cohort studies and the mean age at OAC diagnosis was 64 years. Approximately 82.1% of the patients with BO in these studies were men. More than 75% of the patients in the studies were Caucasians. The proportion of patients with long-segment BO (>3 cm) ranged from 29% to 59% when reported[111922]; Kastelein and colleagues only included patients with BO segment length >2 cm.[10] In three studies, there was no information on baseline length of BO segment.[182021] Only three studies reported on the presence of erosive esophagitis in the cohort (present in 9–88% of BO cohort)[101922]; three studies reported on the presence of reflux symptoms (present in 29–77% of cohort).[101822] About 22–58% of patients with BO in the included studies were concomitantly on NSAIDs/aspirin and 19–46% were on statins.

Quality assessment

Overall, the methodological quality of included studies was moderate to high. Online supplementary table S1 describes the quality of included studies. Only three studies accounted for the presence of reflux symptoms or erosive esophagitis,[101819] and only two studies adjusted for concomitant use of other putative chemopreventive medications.[1011] Systematic differences in PPI users and non-users were explored in only two studies[1021]— there were no differences by patient age, sex, presence of obesity, smoking and alcohol use,

characteristics of BO (segment length, baseline dysplasia) or use of NSAIDs/aspirin/statins; however, in one study, PPI users were less likely to have reflux symptoms or esophagitis, and were more likely to have prevalent BO (ie, longer duration of BO).[10]

PPI use and risk of advanced neoplasia in patients with BO

On meta-analysis of six studies that reported the endpoint of OAC and/or BO-HGD, use of PPI at time of BO diagnosis was associated with decreased risk of OAC and/or BO-HGD in patients with BO (unadjusted OR 0.26; 95% CI 0.10 to 0.71). Inclusion of one additional study, which assessed the risk of progression to any grade of dysplasia or OAC in patients with non-dysplastic BO, did not significantly change the results (unadjusted OR 0.27; 95% CI 0.12 to 0.63) (figure 2A). This protective association persisted on using the maximally adjusted risk estimates reported in individual studies, with a 71% lower risk of OAC and/or BO-HGD in PPI users (adjusted OR 0.29; 95% CI 0.12 to 0.79; figure 2B). In four studies, which reported the time to progression to OAC or BO-HGD in a cohort of patients with BO, PPI users were also significantly less likely to progress to OAC or BO-HGD (adjusted HR 0.32; 95% CI 0.15 to 0.67).[10111922] In three studies, which reported the risk of progression to any degree of dysplasia in a cohort of patients with non-dysplastic BO, PPI use was protective (adjusted OR 0.37; 95% CI 0.15 to 0.96).[111921] There was insufficient information in these studies to allow estimation of PPIs' effect on risk of progression to OAC alone and BO-HGD alone.

There was considerable heterogeneity in the overall analysis (I^2=81%), although this was observed primarily due to two case–control studies with divergent results[1820]; on meta-analysis of five cohort studies, the use of PPIs was consistently and strongly associated with a lower risk of any dysplasia in patients with BO (adjusted OR 0.33; 95% CI 0.19 to 0.58; I^2=10%).

Subgroup and sensitivity analysis

The association between PPIs and risk of OAC or BO-HGD was stable across study design and study location (table 3). The heterogeneity observed in the overall analysis could be partly explained based on the method of exposure ascertainment as well as what proportion of patients in the entire BO cohort were on PPIs; statistically significant risk estimates were not noted when >90% of patients in the entire BO cohort were on PPIs.

The independent protective association between PPIs and risk of OAC and/or BO-HGD persisted, even on restricting analysis to studies, which adjusted for the concomitant use of NSAIDs/aspirin/statins (n=2 studies; adjusted OR 0.44; 95% CI 0.24–0.83).[1011] On the others, analysis of the remaining five studies which did not adjust for concomitant use of NSAIDs/aspirin/statins revealed a similar protective association between PPIs and risk of OAC and/or BO-HGD (adjusted OR 0.23; 95% CI 0.06 to 0.89). In three studies, which accounted for the presence of erosive esophagitis or reflux symptoms, use of PPI was still protective against OAC (adjusted OR 0.15; 95% CI 0.04 to 0.55). To assess whether any one study had a dominant effect on the summary OR, each study was excluded and its effect on the main summary estimate was evaluated. No study markedly affected the summary estimate or p value for heterogeneity among the other summary estimates, and the pooled

point estimate remained statistically significant (range 0.22–0.41), with the corresponding 95% CI bounds remaining below 1.

Duration–response relationship

The presence of a duration–response relationship was examined in five studies, of which four studies observed a greater protective effect with longer duration of PPI use.[10 11 18–20] For meta-analysis, we used data from three studies that were conducive for pooling since they divided exposure time intervals as short term (<2–3 years) and long term (>2–3 years);[10 11 20] one of the other studies used a 6-month cutoff[18] and another assessed PPI exposure in terms of delay in starting it after BO diagnosis (eventually, all patients were placed on PPIs in this cohort).[19] Based on these three studies, long-term exposure to PPIs (>2–3 years) was associated with a greater protective effect on OAC and/or BO-HGD risk (adjusted OR 0.45; 95% CI 0.19 to 1.06) whereas short-term exposure (<2–3 years) was not significantly associated with OAC and/or BO-HGD (adjusted OR 1.09; 95% CI 0.47 to 2.56).

There were insufficient data to allow pooling based on type, dose or frequency of use of PPIs. One study reported that the protective association of PPIs was seen at all doses, with all types and regardless of whether they were used once a day or twice a day.[10] In the same study, however, the importance of adherence to PPI for the chemopreventive effect was highlighted—compared with patients who filled <90% of their PPI prescription, patients with BO who filled >90% of their PPI prescription had a significantly greater reduction in risk of progressing to OAC and/or HGD (adjusted HR 0.24; 95% CI 0.08 to 0.71).

Number needed to treat

The observed cumulative incidence rates of OAC and/or BO-HGD in patients with BO overall, non-dysplastic BO and BO-LGD are 10.2, 6.8 and 18.3 per 1000 patient years, respectively.[22 28 29] Using a 67% summary risk reduction of OAC and/or BO-HGD with PPI use in patients with BO, derived from cohort studies (with low heterogeneity), we estimate the number needed to treat with PPIs to prevent one case of OAC or BO-HGD in these patients at 147, 220 and 82, respectively.

Histamine-receptor antagonist use and risk of advanced neoplasia in patients with BO

Two studies reported on the association between H2RA use and the risk of OAC in patients with BO (156 cases of OAC in 1352 patients with BO; 25.4% were on H2RAs).[10 20] None of the studies individually observed a protective association. However, in one study all but one H2RA user were also on PPIs concomitantly and hence it was not possible to adequately assess the independent association between H2RA use and risk of advanced neoplasia in patients with BO[10] ;in this study, H2RA use was not significantly associated with decreased risk of progression to advanced neoplasia (adjusted HR 0.83; 95% CI 0.11 to 6.03). In the other study, only unadjusted analysis on the association between H2RA use and risk of OAC was presented (unadjusted OR 1.17; 95% CI 0.78 to 1.76).[20] Given these limitations, a meta-analysis on the association between H2RAs and risk of OAC and/or BO-HGD in patients with BO was not performed.

DISCUSSION

In this systematic review of all published studies in 2813 patients with non-dysplastic BO (or BO-LGD), of whom 317 progressed to OAC and/or BO-HGD, we observed that PPI use was associated with a 71% risk reduction in progression to OAC and/or BO-HGD in a duration-dependent manner—PPI use >2–3 years after BO diagnosis was associated with a lower risk of OAC and/or BO-HGD, whereas PPI use for <2–3 years was not associated with a protective effect. This association was consistent and stable in cohort studies, which are at low risk of recall bias. In addition, we observed an association between PPI and risk of OAC and/or BO-HGD in patients with BO, independent of the presence of erosive esophagitis or reflux symptoms, and independent of the concomitant use of NSAIDs/aspirin and statins, albeit in a small number of studies. However, there is limited information in only two studies on the association between H2RA use and risk of OAC and/or BO-HGD in patients with BO, and a meaningful conclusion on their potential chemopreventive effect could not be drawn.

Given the high incidence and mortality from OAC, chemo-preventive agents are highly desirable.[3–5] Our findings of an estimated 71% risk reduction in OAC and/or BO-HGD are similar to those observed in a previous small limited systematic review of three of these studies, published as a letter to the editor.[30] However, in that review there was no quantitative synthesis, assessment of quality of included studies, and no subgroup or sensitivity analyses. Aspirin and statins have also been proposed as effective agents associated with a lower risk of OAC and/or BO-HGD in patients with BO, but the effect size is moderate, with a 32–41% estimated risk reduction.[3132]

Antineoplastic effect of PPI therapy

The primary hypothesised chemopreventive mechanism of PPIs is by decreasing intra-oesophageal acid and bile exposure, thus promoting oesophageal mucosal healing. Intermittent exposure to acid has been shown to induce epithelial proliferation in vivo and in vitro.[33] Acid and bile exposure have also been shown to upregulate cyclooxygenase-2 (COX-2) expression in BO, which has been implicated in oesophageal carcinogenesis.[3435] Complete, but not partial, acid suppression by PPIs over 6 months as measured by 24 h pH monitoring, decreases markers of epithelial proliferation and increases cell differentiation markers in patients with BO.[36] PPIs also decrease duodeno-gastroesophageal reflux, protecting the metaplastic epithelium from bile acid induced injury.[7] PPIs also have anti-inflammatory properties independent of their acid-suppressive effects, and this may also contribute to their chemopreventive effect against OAC.[37] In addition, long-term aggressive PPI therapy induces the formation of oesophageal squamous islands in patients with BO[738] and may decrease the length of the BO segment, though this association is inconsistent.[71039] However, clinical studies have been inconclusive on whether PPI causes regression of established dysplasia in patients with BO, although these studies have typically involved only a short duration of PPI therapy (<6 months), have enrolled small numbers of patients with dysplasia, and have had short-term follow-up to allow estimation of progression to OAC and/or BO-HGD.[7] A recent phase II chemoprevention trial demonstrated that a combination of high-dose aspirin (325 mg/day) with esomeprazole decreases levels of

prostaglandin E2, a marker of resistance to apoptosis, increased angiogenesis and enhanced invasion in BO mucosa.[6]

There has been a theoretical concern that prolonged acid suppressive therapy with PPIs can induce hypergastrinemia, which may induce proliferation, COX-2 upregulation, potentiating oesophageal carcinogenesis.[840] However, Obszynska and colleagues demonstrated that, though gastrin enhances epithelial restitution in Barrett's mucosa, it does not promote proliferation and expansion of Barrett's segments during long-term PPI treatment.[4142] Hence, there is no evidence from preclinical and clinical studies that prolonged therapy with PPIs promotes oesophageal carcinogenesis, and this was also borne out in our review.

Strengths and limitations

The strengths of this systematic review include the following: comprehensive and systematic literature search with well defined inclusion criteria, carefully excluding redundant studies; rigorous evaluation of study quality; subgroup and sensitivity analyses to evaluate the stability of findings and identify potential factors responsible for inconsistencies; assessment of duration–response relationship using a fairly stable 2–3-year cutoff from included studies; simultaneous evaluation of unadjusted (based on raw numbers) and adjusted risk estimates, and hence, being able to evaluate the potential influence of measured confounders on the summary estimate; and low likelihood of misclassification bias since the included studies rigorously defined BO, often being reviewed by two or at least one expert gastrointestinal pathologist.

There are several limitations in our study. First, the meta-analysis included only observational studies. No RCTs have been performed to explore this association. Observational studies lack the experimental random allocation of the intervention necessary to test exposure–outcome hypotheses optimally. Since >80% of the patients in the included studies were on PPIs at the time of BO diagnosis (and more patients were eventually prescribed PPIs during follow-up), it is difficult to tease out the exact efficacy of these agents in decreasing neoplastic progression in patients with BO. Despite adjusting for several covariates, it is not possible to eliminate the potential of residual confounding, especially with regard to factors that go into acid-suppressive medication prescription in patients with BO. It is possible that patients with endoscopic findings of severe erosive esophagitis (who are more likely to progress to OAC) were more likely to be prescribed PPIs, thereby spuriously weakening the observed association (confounding by severity of disease). However, it is possible that health-conscious patients with ready access to healthcare may be more likely to be prescribed PPIs, thereby spuriously strengthening the observed association (healthy user bias). Additionally, most of the included studies did not account for several potential confounding factors, including obesity and smoking, which influence exposure and outcome. However, using the adjusted data for any use of PPIs had little effect on the summary OR, suggesting that any difference attributable to using different confounders for adjustment is likely small. Second, considerable heterogeneity was observed in the overall analysis; however, this was primarily attributable to two case–control studies with disparate results—meta-analysis of cohort studies resulted in a consistent result with very low heterogeneity (I^2=9%). Although six of the included studies reported a lower

risk of OAC and/or BO-HGD with PPI use (four were statistically significant), one large nested case–control study did not observe any association between PPIs and risk of OAC.[20] In this study, ~95% of the entire cohort of patients with BO were on PPIs and the majority (>80%) of these included cases and controls had been on PPIs for <2 years. Baseline dysplasia status of control patients with BO was not available. This may have resulted in an inability to identify a significant association between PPIs and OAC risk in this study. Third, we were unable to rule out the presence of a publication bias. With such limited number of studies, statistical testing for publication bias assessment is not recommended.[17] We tried to minimise the potential for this by carefully examining published abstracts. Finally, the included studies had inherent limitations. Three of the studies were performed in the military veteran population, which is overwhelmingly male and tends to have higher prevalence of smoking and metabolic syndrome, both of which are associated with greater risk of progression to OAC. Additionally, in our analysis, the majority of patients were older men; our results would require independent validation in the general population, particularly women. Except for one study, there was inadequate information on medication compliance.[10] Moreover, there was insufficient information on the efficacy of PPIs in acid suppression. A definite dose of PPI required for chemopreventive effect is unclear; only one study assessed different doses and types of PPIs and did not report significant differences in risk estimates.[10]

Implications for clinical practice

While PPIs are routinely recommended for management of GERD, we believe, based on the results of this systematic review, that in patients with BO with multiple risk factors for progression to OAC and/or BO-HGD (such as long-segment BO, BO-LGD, central adiposity, smoking, advanced age), PPI therapy should be considered for its primary chemopreventive potential. While an exact dose and therapeutic efficacy endpoint are not known, a regular once-daily dose of PPI therapy may be appropriate. There is no clinical evidence supporting the notion that PPI therapy may increase the risk of neoplastic progression in patients with BO. Furthermore, a cost-effectiveness analysis comparing six strategies of chemoprevention in BO (no drugs, generic PPI, brand name PPI (both estimating a 50% risk reduction in neoplastic progression), chemoprevention drug (estimating a 35% reduction in risk), or a combination of generic or brand name PPI with chemoprevention drug) identified use of a generic PPI as the most cost-effective strategy for the prevention of OAC in patients with BO.[43] However, given the concerns about side effects and potential long-term risks associated with chronic PPI use, the risks and benefits would need to be carefully discussed with patients.[44]

CONCLUSIONS

Based on a systematic review and meta-analysis of all existing studies, PPI therapy is associated with a significantly decreased risk of progression to OAC and/or BO-HGD in patients with BO. Long duration (>2–3 year) of PPI use may provide a greater benefit than short duration. The effect of PPI therapy seems to be independent of NSAID/aspirin/statin use or the presence of erosive esophagitis. There is insufficient evidence to assess whether H2RAs have an independent chemopreventive effect in patients with BO.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Significance of this study

What is already known about this subject?

- The incidence of oesophageal adenocarcinoma (OAC) is rising and it is associated with high mortality.
- Barrett's oesophagus (BO), which is a result of chronic inflammation of the oesophagus, confers a significant increased risk of OAC.
- Acid-suppressive medications, particularly proton pump inhibitors (PPIs), decrease the risk and severity of erosive esophagitis and gastroesophageal reflux disease.

What are the new findings

- PPIs are associated with a 71% decrease in the risk of progression to OAC and/or high-grade dysplasia in patients with BO.
- This effect of PPIs is typically seen after 2–3 years of use and is independent of the presence of erosive esophagitis and use of other putative chemopreventive agents like aspirin and statins.
- There is insufficient literature to assess whether histamine receptor antagonists modify the risk of OAC in patients with BO.

How might it impact on clinical practice in the foreseeable future?

- In patients with BO at high risk of progression to OAC, PPI therapy may be considered for its primary chemopreventive potential.

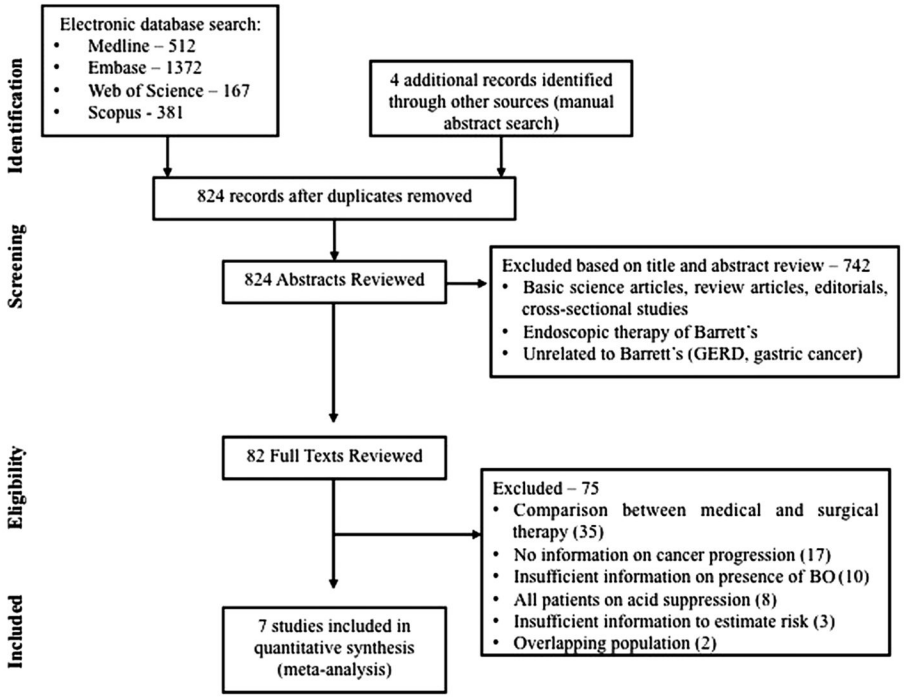

Figure 1.

Flow sheet summarising study identification and selection. BO, Barrett's oesophagus; GERD, gastroesophageal reflux disease.

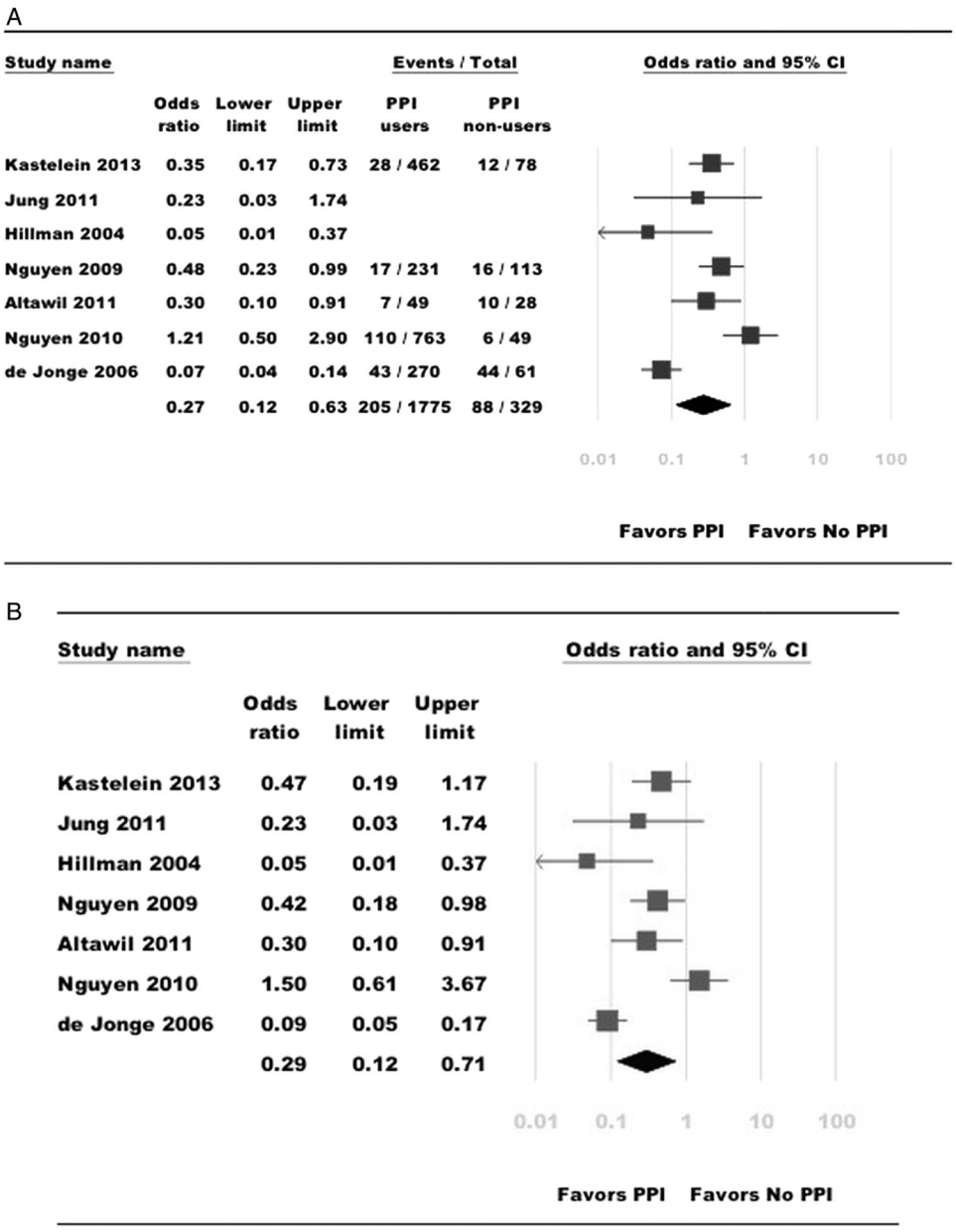

Figure 2.

(A) Summary of *unadjusted* ORs assessing the risk of oesophageal adenocarcinoma (OAC) and/or high-grade dysplasia (HGD) in patients with Barrett's oesophagus (BO) with proton-pump inhibitor (PPI) exposure in all included studies. The size of the box corresponds to the weight of the given study. (B) Summary of *adjusted* ORs assessing the risk of OAC and/or HGD in patients with BO with PPI exposure in all included studies. The size of the box corresponds to the weight of the given study.

Table 1

Characteristics of individual studies included in the meta-analysis

First author, ref.	Location; setting	Time period; follow-up	Total no. of patients with BO with baseline dysplasia status	Incident OAC and/or HGD	Primary outcome of interest	Patients on PPI		Patients not on PPI		Variables adjusted for
						Incident OAC and/or HGD	Total no. of patients on PPI	Incident OAC and/or BO-HGD	Total no. of patients not on PPI	
Cohort studies										
Kastelein[10]	Rotterdam, The Netherlands; multicentre, hospital based	2003–2009; mean 5.2 years	540 NDBO—86% LGD—14%	HGD—28 OAC—12 Combined—40	Progression to OAC and/or HGD	28	462* (85.6%)	12	78 (14.4%)	1, 2, 7, 8, 9, 10, 11
Jung[22]	Minnesota, USA; population based	1976–2006; median 5.9 years	355 NDBO—83% LGD—17%	HGD—12 OAC—7 Combined—9	Progression to OAC and/or HGD	Univariate HR for progression to OAC and/or HGD, for PPI users (PPI non-users as reference): 0.23 (95% CI 0.03 to 1.72)				N/A
Hillman[19]	Canberra, Australia; 2 centres, hospital based	1981–2001; median 7.4 years	350† NDBO—85.4% LGD—14.6%	HGD—9 OAC—7 Combined—11	Progression to OAC and/or HGD	216 (61.7%) on PPI at start of surveillance; during follow-up all patients started on PPI; using time to PPI use as a time-dependent covariate, >2-year delay in starting PPI after BO diagnosis, resulted in 21-fold higher risk of OAC and/or HGD compared with use at time of BO diagnosis (HR 20.9; 95% CI 2.78 to 158)				1, 2, 10
Nguyen[11]	Arizona, USA; multicentre, hospital based	1982–2004; mean 7.6 years	344 NDBO—100% LGD—0	HGD—20 OAC—13 Combined—33	Progression to OAC and/or HGD	17	231 (67.2%)	16	113 (32.8%)	1, 2, 7, 11
Altawil[21] (abstract)	Michigan, USA; single centre, hospital based	2004–2010; NR	77 NDBO—100% LGD—0	17 (any dysplasia or OAC)	Progression to OAC and/or HGD and/or LGD	7	49 (63.6%)	10	28 (26.4%)	NR
Case–control studies										
Nguyen[20] (nested case-control study)	Nationwide VA, USA; multicentre, hospital based	2000–2002; NA	812	OAC—116	Development of OAC	110	763 (94.0%)	6	49 (6.0%)	1, 2, 3, 9, 12, 13, 14
de Jonge[18]	Rotterdam, The Netherlands; multicentre, hospital based	2003–2005; NA	335	OAC—91	Development of OAC	43	270 (81.6%)	44	61 (18.4%)	1, 2, 4, 5, 10

Variables adjusted for age, sex, race, smoking, alcohol use, obesity, BO length, baseline dysplasia status, time of BO diagnosis, esophagitis or reflux symptoms, medications (NSAIDs/aspirin/statins), healthcare encounters, comorbidities, socioeconomic status; studies arranged by study design, and within OAC study type, by size of BO cohort.

*A total of 462 patients were on PPI at time of enrolment in cohort, with an additional 70 patients starting PPI during surveillance.

†Only 299 patients with NDBO used for analysis.

BO, Barrett's oesophagus; HGD, Barrett's oesophagus with high-grade dysplasia; LGD, Barrett's oesophagus with low-grade dysplasia; NA, not applicable; NDBO, non-dysplastic Barrett's oesophagus; NR, not reported; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; OAC, oesophageal adenocarcinoma.

Table 2

Baseline characteristics of patients in the included studies

First author, ref.	Age at BO diagnosis	Sex (% men)	Race (% Caucasian)	Obesity (% with BMI >30 kg/m^2)	Smoking (% smokers)	Length of BO (% with LSBO)	Reflux symptoms or; endoscopic esophagitis	Other medication use	
								NSAIDs/aspirin	Statins
Cohort studies									
Kastelein[10]	61 (53–68)	71	NR	19	19 (current)	100*	29%; 9%	110 (20.4%)	102 (18.9%)
Jung[22]†	63 (14)	69	NR	29‡	13 (current)	59	77%; 31%	NR	NR
Hillman[19]	58 (12)	71	NR	NR	NR	45.0	NR; 88%	78 (22.0%)	NR
Nguyen[11]	61 (12)	94	90	NR	NR	29.1	NR	169 (49.1%)	87 (25.3%)
Altawil[21]	60	96	75	28.9§	NR	NR	NR	20 (26.0%)	27 (35.1%)
Case–control studies									
Nguyen[20]	65 (10)¶	97	74	NR	NR	NR	NR	468 (57.6%)	377 (46.4%)
de Jonge[18]	62 (11)¶	74	100	27	20	NR	72.5%; NR	134 (40.0%)	NR

*All patients with BO segment ≥2 cm.

†For entire cohort of patients with BO.

‡Mean BMI.

§Mean BMI among PPI users.

¶Age at OAC diagnosis or age of corresponding controls.

BMI, body mass index; BO, Barrett's oesophagus; LSBO, long-segment Barrett's oesophagus; NR, not reported; NSAID, non-steroidal anti-inflammatory drug. OAC, oesophageal adenocarcinoma; PPI, proton pump inhibitors

Table 3

Subgroup analyses and dose–response relationship on the association of PPI use and risk of OAC and/or BO-HGD in patients with BO

Groups	Categories	No. of studies	Adjusted OR	95% CI	Heterogeneity within groups (I^2)	$P_{interaction}$
Study design	Case–control	2	0.36	0.02 to 5.67	96%	0.96
	Cohort	5	0.33	0.19 to 0.58	9%	
Study location	USA	4	0.52	0.22 to 1.53	57%	0.11
	Non-USA	3	0.15	0.04 to 0.55	80%	
Proportion of patients on PPI	>90%	1	1.50	0.61 to 3.67	–	<0.01
	<90%	6	0.22	0.09 to 0.50	74%	
Method of exposure assessment	Pharmacy prescription records	3	0.66	0.30 to 1.47	59%	<0.01
	Medical records	3	0.19	0.07 to 0.52	16%	
	Self-report	1	0.09	0.05 to 0.17	–	
Duration–response	<2–3 years	3	1.09	0.47 to 2.56	48	0.15
	>2–3 years	3	0.45	0.19 to 1.06	44	

BO, Barrett's oesophagus; HGD, Barrett's oesophagus with high-grade dysplasia; OAC, oesophageal adenocarcinoma; PPI, proton pump inhibitor.