

Risk of Esophageal Adenocarcinoma in Patients With Barrett's Esophagus Using Proton Pump Inhibitors: A Systematic Review With Meta-Analysis and Trial Sequential Analysis

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Abstract

Background: Proton pump inhibitors (PPIs) have been used to treat Barrett's esophagus (BE), but there seems to be insufficient evidence that PPIs can prevent esophageal adenocarcinoma (EAC) and high grade dysplasia (HGD). This study aimed to evaluate the effects of PPIs in BE patients.

Methods: PubMed and EMBASE were systematically searched. Stata13 and trial sequential analysis (TSA) software were used to carry out related statistics. Pooled odds ratio (OR) with 95% confidence intervals (CIs) were calculated.

Results: Using PPIs to reduce the incidence of EAC and HGD has not been confirmed (OR, 0.61; 95% CI, 0.29–1.26). The pooled results of three cohort studies reported that PPIs use was protective (OR 0.48; 95% CI 0.33 to 0.70). But the pooled results of five case-control study indicating PPIs use does not prove this protective effect (OR 0.73; 95% CI 0.21 to 2.48). On pooled analysis of 4 US studies 2 Netherlands, protective effect on development of EAC and HGD was noted (OR, 0.59; 95% CI, 0.43–0.80) and (OR, 0.16; 95% CI, 0.03–0.75).

Conclusion: According to the Meta analysis and TSA of existing studies, the protective effect of PPIs on the progression of BE patients to OAC and / or HGD has not been confirmed. TSA shows that more patients are needed before a clear conclusion can be reached.

Background

Esophageal adenocarcinoma (EAC) and high grade dysplasia (HGD) are thought to occur through gastroesophageal reflux. Barrett's esophagus (BE) is one of the steps on adverse events occur. BE means that the squamous epithelium of the lower part of the esophagus is covered by columnar epithelium. And reducing gastric acid that results from proton pump inhibitors (PPIs) can slow up this process. The incidence of EAC has increased¹. At present, PPIs is recommended for the treatment of BE, but the evidence about using PPIs to prevent the progression from BE to HGD and EAC seem to be insufficient. Several studies reported that use of PPIs may decrease the risk of HGD or/and EAC^{2,3}. In contrast, there were some studies showed an increase in risk of HGD or/and EAC with PPIs use^{2,4}. The effects of PPIs on the risk of EAC and HGD in patients with BE remain controversial. Therefore, this paper will use meta-analysis and trial sequential analysis (TSA) to explain it more objectively.

Methods

Data sources, search strategy and study selection

This study complies with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement⁵. PubMed and EMBASE were searched through June 7, 2020, and some studies were manually searched to get more information. Comprehensive search terms were listed in Appendix 1. All studies were selected by two independent reviewers (Lunan Li and Huiqin Gao). The article can be

included as long as it reported relative risk (RR) or odds ratio (OR), or provided data for their calculation, but the conferences were excluded. Inclusion was not otherwise restricted by study size or language. Group discussion were carried out in cases of disagreement.

Data extraction and quality assessment

Data sets were extracted by two independent reviewers (Lunan Li and Huiqin Gao) from each included study. The required information included the first authors name, publication year, country, age, sex, and research type. Any dispute was discussed to maintain a consistent result. The quality was independently assessed by two authors (Lunan Li and Huiqin Gao) using the Newcastle–Ottawa scale (NOS)^{6,7}. Any discrepancies were discussed in our group.

Data analysis

Stata13 was used for statistical analyses. TSA program version 0.9 beta was conducted to control random errors and evaluate inaccuracies. The heterogeneity was calculated with I^2 statistic, and the value greater than 75% indicated that there has considerable heterogeneity⁸. When heterogeneity was present, the random-effects model was described by DerSimonian and Laird to calculate summary OR and 95% confidence intervals (CIs)⁹. Subgroup analysis were calculated that the result in different study types and countries. TSA is used to estimate the amount of information needed for the meta-analysis of conclusions, and to evaluate whether the results have type I errors due to the insufficient number of studies included. There is a risk of random errors in conventional meta-analysis due to sparse data and repeated tests¹⁰. The TSA depends on the quantification of the amount of information required. The random-effects model was used for our study. We calculated the OR with 95 % CI for each included trial. The purpose of TSA is to keep the overall risk of type I errors at 5% and the power at 80%. For the calculation of the required information size, we expect to use 11% of the event incidence in the control group for meta-analysis.

Results

The study selection process is shown in Figure 1. 8 studies (three cohorts, five case–control studies) with 7053 patients were included^{2,11-17}. The characteristic of each study are presented in Table 1. The quality of the methodology included in the study ranges from medium to high (table 2).

Meta-analysis of eight studies in patients with BE revealed that use of PPIs to reduce the incidence of EAC and HGD has not been confirmed (OR, 0.61; 95% CI, 0.29–1.26) in statistics. The results showed significant heterogeneity with the corresponding $I^2=89.7%$ (Figure 2). The association between PPIs and the progression of OAC or HGD in BE patients was unstable in study design and study location. In three cohort studies, which reported the risk of BE patient progression to HGD and EAC, PPIs use was protective (OR 0.48; 95% CI 0.33 to 0.70), and the corresponding $I^2=0.0%$ (Figure 3). However, five case-control study with 5144 BE patient indicating PPIs use does not prove this protective effect (OR 0.73; 95% CI 0.21 to

2.48) and there was considerable heterogeneity ($I^2=94.0\%$) (Figure 3). In the subgroup analysis, on pooled analysis of 4 US studies, a protective effect on development of EAC and HGD was noted (OR, 0.59; 95% CI, 0.43–0.80), and the corresponding $I^2=3.2\%$ (Figure 4). Meta-analysis of the 2 studies reported on Netherlands that assessed the effect of PPIs use on the development of EAC and HGD in BE (OR, 0.16; 95% CI, 0.03–0.75) with $I^2=90.2\%$ (Figure 4).

TSA (Figure 5) showed that the trial monitoring boundary for benefit was not crossed. The TSA of all trials showed that the amount of information accumulated was far from the amount of information needed, and that more than 13560 patients might needed to draw firm conclusions. The overall pooled results showed no statistical difference (random-effects model OR 0.61, 95 % CI 0.29–1.26).

Discussion

In the Meta analysis of 7053 patients, the use of PPIs to reduce the risk of HGD and / or EAC in BE has not been confirmed, despite significant heterogeneity in the study. Our results are consistent with previous system assessments¹⁸. In our analysis, we added additional research to provide a more reliable and comprehensive estimate of the impact of EC risk. With the increase of the number of participants, TSA were conducted to evaluate the statistical value of the statistical results and guide further research.

Barrett's esophagus (BE) is one of the complications of gastroesophageal reflux disease (GERD). Therefore, it is generally used to reduce gastric acid to treat patients with BE or GERD. Acid exposure has also been shown to up-regulate the expression of cyclooxygenase-2 (COX-2) in Barrett's esophagus (acid). COX-2 expression is increased during the early development of many tumors, including EAC, and is closely related to the development of BE into esophageal adenocarcinoma^{19,20}. Meta-analysis showed that the use of COX inhibitors was negatively correlated with the risk of tumor progression in patients with BE²¹. But the protective effect has been controversial. Some studies shown that there are contradictory results between the use of H2RA and the development of HGD or EAC. Even a lot of studies reported that it increases the risk of HGD or EAC^{4,22}. Bile exposure has also been shown to up-regulate the expression of COX-2 in BE²³. The main preventive mechanism of PPIs is to promote the healing of esophageal mucosa by reducing esophageal acid and bile exposure.

The results of this study suggest that there was no definite evidence that PPIs intervention improved the incidence of esophageal cancer in patients with BE. The results of cohort study are different from case-control study. One potential explanation for this result is immortal time bias²⁴. It can be produced in cohort studies. When it occurs, there may be an illusion of therapeutic effect in some studies. PPIs has been shown to improve GERD in patients²⁵. But whether the treatment of Barrett's esophagus with PPIs reduces the risk of cancer is worth considering. Endoscopic therapy has been shown to effectively eliminate dysplasia and metaplastic epithelium and greatly reduce the incidence of cancer in a number of randomized controlled trials. There are many treatments for BE, such as radiofrequency ablation, argon plasma coagulation, photodynamic therapy, endoscopic mucosal resection and so on. The presence of nodules, ulcers or strictures in the esophageal segment of Barrett is thought to be associated with an

increased risk of EAC²⁶. Once it happens, the adverse effect on patients may be minimized by choosing to remove the lesion rather than medication.

There are limitations in this paper. First, the relationship between PPIs dose, the time of PPIs use and the occurrence of adverse events are not conducted. Second, due to the limited number of studies we analyzed, publication bias assessment was not conducted²⁷. However, we conducted TSA to show more intuitively that the treatment of BE by PPIs is still controversial and worthy of further exploration.

Conclusion

According to the Meta analysis and TSA of existing studies, the protective effect of PPIs on the progression of BE patients to OAC and / or HGD has not been confirmed. TSA shows that more patients are needed before a clear conclusion can be reached.

Abbreviations

PPIs=Proton pump inhibitors; EAC= Esophageal adenocarcinoma; HGD= High grade dysplasia; BE= Barrett's esophagus; TSA= Trial Sequential Analysis; RR= Relative risk; OR= Odds ratio; NOS= Newcastle–Ottawa scale; GERD= Gastroesophageal reflux disease; COX-2= Cyclooxygenase-2; RIS= Required Information Size

Declarations

Ethics approval and consent to participate: None.

Consent for publication: All authors agree.

Availability of data and material: All have been uploaded.

Competing interests: None.

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Authors' contributions: The research team (all authors) participated in the entire research process to varying degrees.

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Tables

Table 1. Characteristics of studies included in meta-analysis and Trial Sequential Analysis

| author | year | country | Patients on PPI | | Patients not on PPI | | research type |
|---------------|------|--------------------|-----------------|-------|---------------------|-------|--------------------|
| | | | EAC and/or HGD | total | EAC and/or HGD | total | |
| De Jonge PJF | 2006 | Netherlands | 43 | 270 | 44 | 61 | case-control study |
| Nguyen DM | 2009 | America | 17 | 231 | 16 | 113 | cohort study |
| Nguyen DM | 2010 | America | 110 | 763 | 6 | 49 | case-control study |
| Kastelein F | 2013 | Netherlands | 28 | 462 | 12 | 78 | cohort study |
| Hvid-Jensen F | 2014 | Denmark | 134 | 1306 | 6 | 131 | case-control study |
| Maslee GM | 2015 | UK and Netherlands | 46 | 1005 | 11 | 461 | case-control study |
| Thota PN | 2017 | America | 32 | 701 | 25 | 324 | cohort study |
| Tan MC | 2018 | America | 270 | 1024 | 30 | 74 | case-control study |

Table 2. Quality assessment of studies included in meta-analysis and Trial Sequential Analysis

| study | year | Study quality (NOS) | | | Overall quality score (maximum 9) |
|---------------|------|---------------------|---------------|------------------|-----------------------------------|
| | | Selection | Comparability | Outcome/Exposure | |
| De Jonge PJF | 2006 | *** | ** | ** | 7 |
| Nguyen DM | 2009 | **** | ** | *** | 9 |
| Nguyen DM | 2010 | **** | ** | ** | 8 |
| Kastelein F | 2013 | **** | ** | *** | 9 |
| Hvid-Jensen F | 2014 | **** | ** | *** | 9 |
| Masclee GM | 2015 | **** | ** | *** | 9 |
| Thota PN | 2017 | *** | ** | *** | 8 |
| Tan MC | 2018 | **** | ** | ** | 8 |

Figures

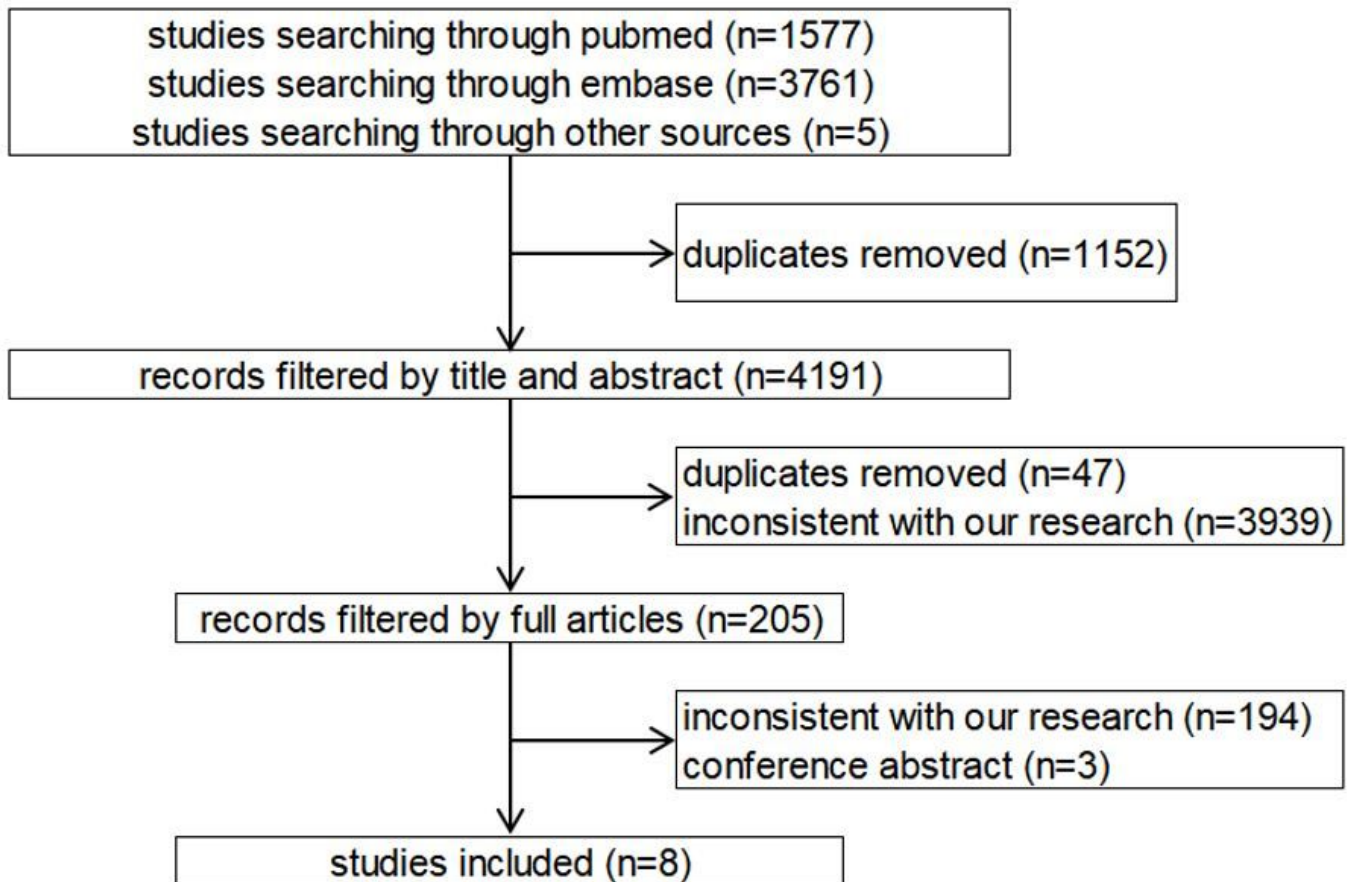


Figure 1

Flow diagram

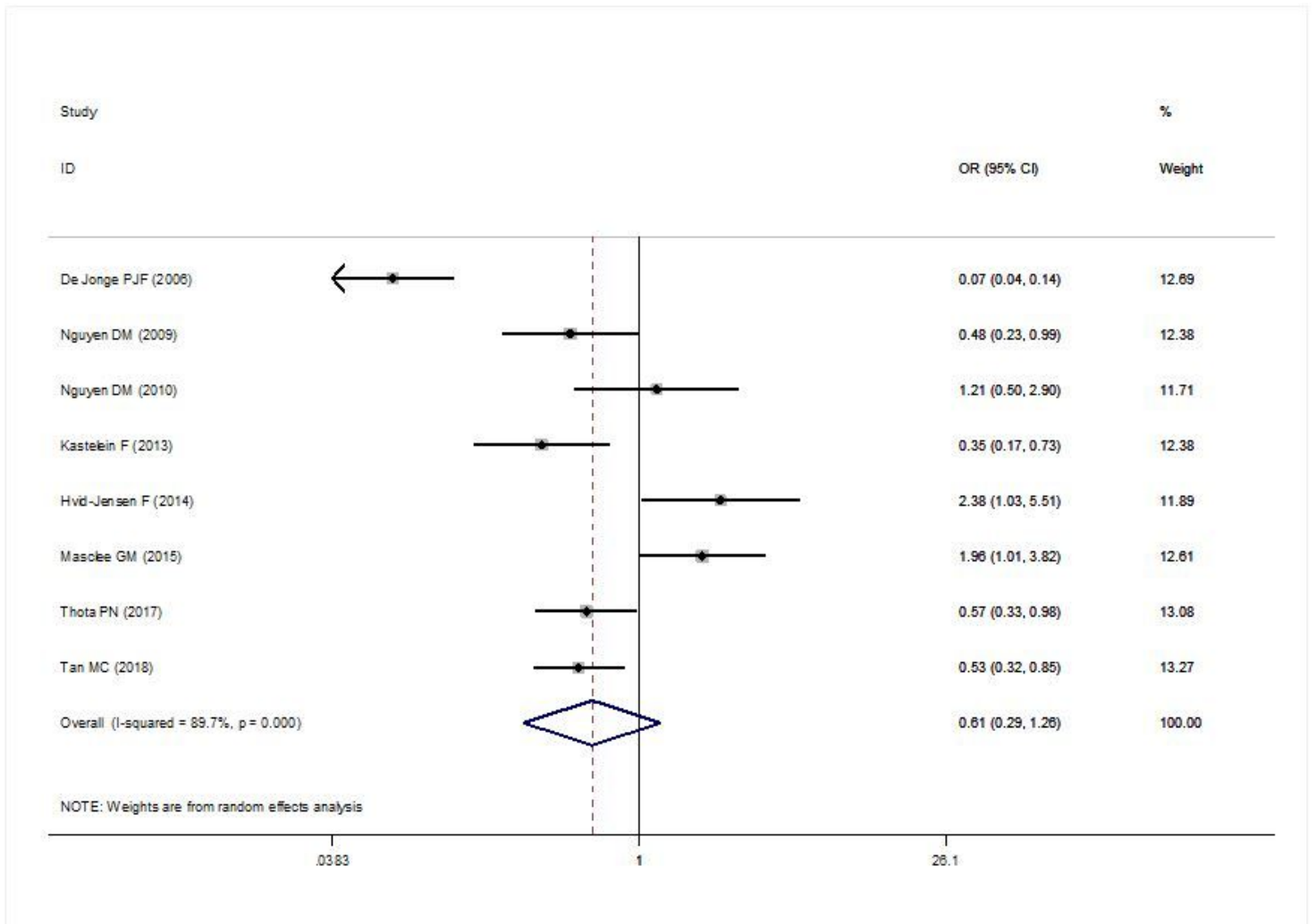


Figure 2

Pooled of the risk of EAC and/or HGD in patients with BE with PPIs exposure in included studies.

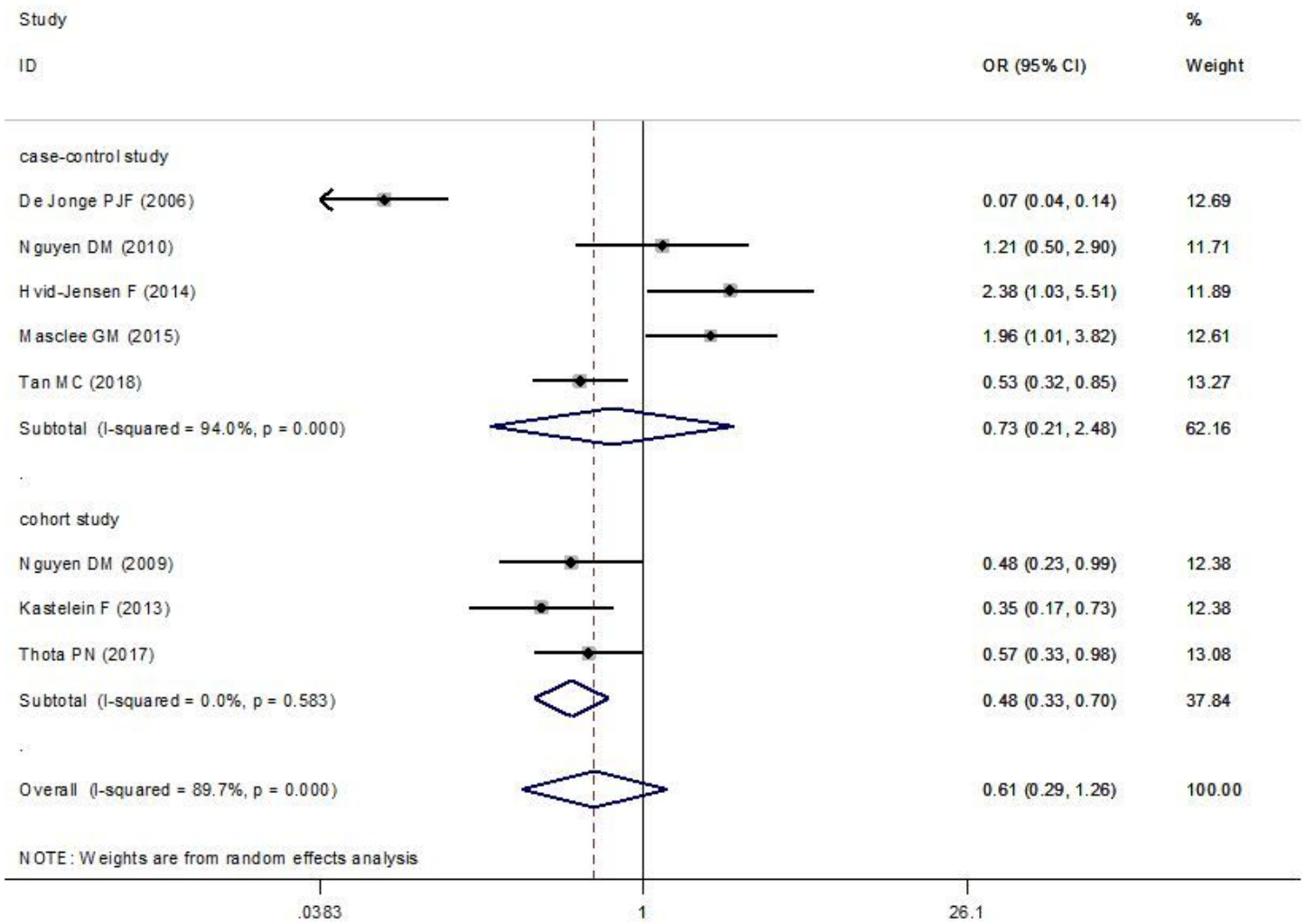


Figure 3

Subgroup analysis of the risk of patients EAC and/or HGD in patients with BE

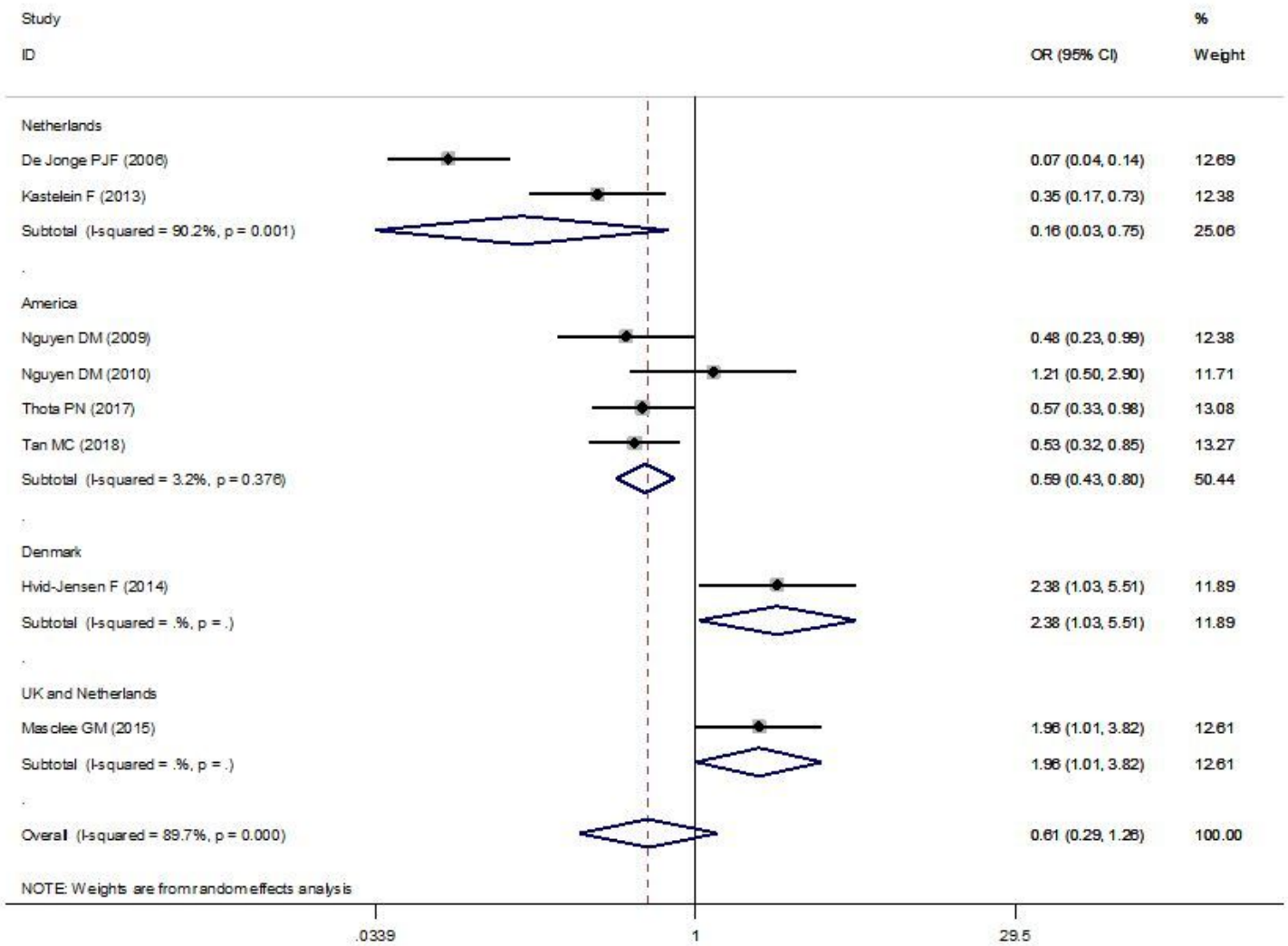


Figure 4

Subgroup analysis of the risk of patients EAC and/or HGD in patients with BE

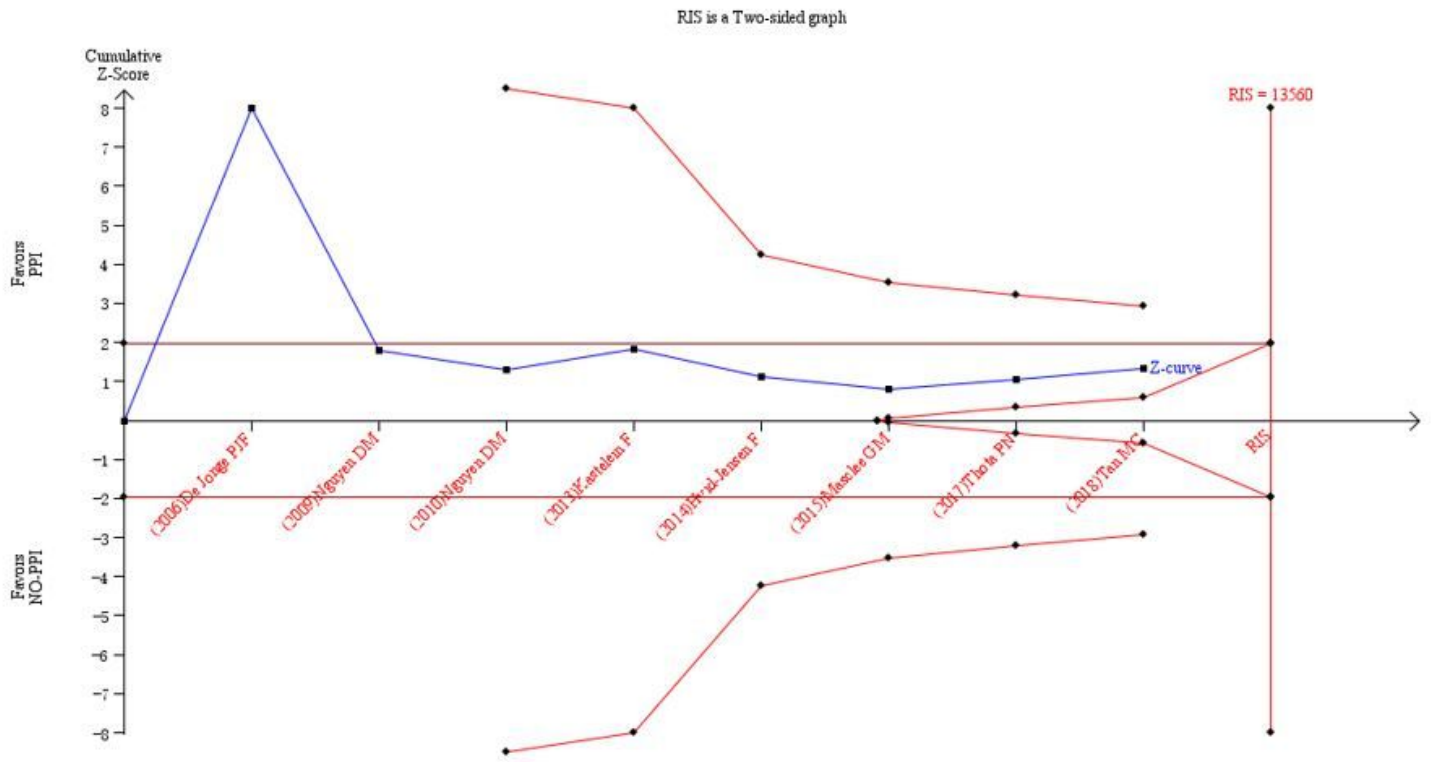


Figure 5

Trial Sequential Analysis of PPIs use and risk of EAC and/or HGD in patients with BE. RIS, Required Information Size.

Supplementary Files

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