Proton pump inhibitors in esophageal atresia: A systematic review and meta-analysis

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REVIEW ARTICLE

Review Article

Proton pump inhibitors in esophageal atresia: A systematic review and meta-analysis

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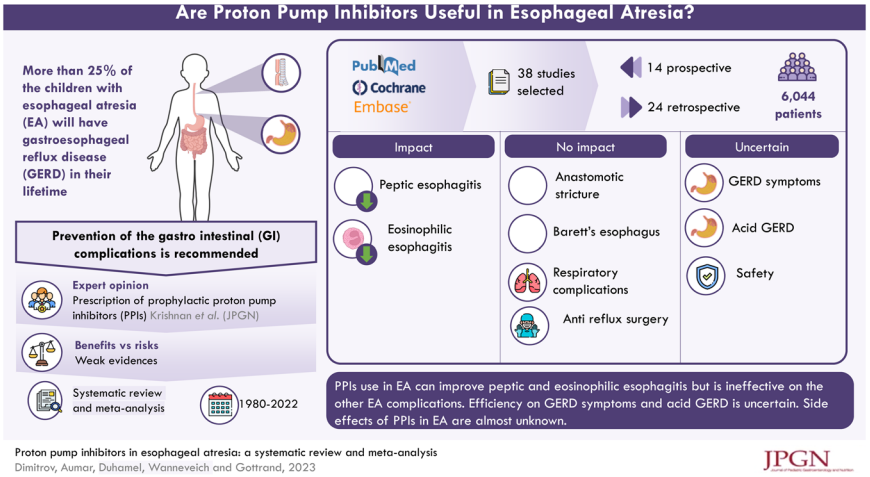
Abstract

Gastroesophageal reflux disease (GERD) is frequent and prolonged in esophageal atresia (EA) pediatric patients requiring routine use of proton pump inhibitors (PPIs). However, there are still controversies on the prophylactic use of PPIs and the efficacy of PPIs on GERD and EA complications in this special condition. The aim of the study is to assess the prophylactic use of PPIs in pediatric patients with EA and its complications. We, therefore, performed a systematic review including all reports on the subject from 1980 to 2022. We conducted meta-analysis of the pooled proportion of PPI—and no PPI groups using random effect model, meta-regression, and estimate heterogeneity by heterogeneity index I^2. Thirty-eight reports on the topic met the criteria selection, representing a cumulative 6044 patients with EA. Prophylactic PPI prescription during the first year of life does not appear to prevent GERD persistence at follow-up and is not associated with a significantly reduced rate of antireflux surgical procedures (ARP). PPIs improve peptic esophagitis and induce remission of eosinophilic esophagitis at a rate of 50%. Their effect on other GERD outcomes is uncertain. Evidence suggests that PPIs do not prevent anastomotic stricture, Barrett's esophagus, or respiratory complications. PPI use in EA can improve peptic and eosinophilic esophagitis but is ineffective on the other EA complications. Side effects of PPIs in EA are almost unknown.



KEYWORDS
anastomotic stricture, Barrett's esophagus, child, eosinophilic esophagitis, gastroesophageal reflux disease

1 | INTRODUCTION

Esophageal atresia (EA) is the most frequent congenital esophageal malformation accounting for 1.8–2.4 cases per 10,000 births. Despite good survival, short- and long-term morbidities are significant.[1–3] Gastroesophageal reflux disease (GERD) affects more than 50% of patients in their lifespan and is involved in the pathophysiology of most EA complications: anastomotic stricture, peptic esophagitis, Barrett's esophagus, feeding disorders, increasing dysmotility, respiratory problems, and decreased quality of life.[1,3] Therefore, antiacid therapy, mainly proton pump inhibitors (PPIs), is widely prescribed to prevent or treat complications. PPIs are also prescribed in eosinophilic esophagitis (EoE), which is frequently associated with EA.[3,4] PPIs prescription in EA has been addressed in the ESPGHAN-NASPGHAN Guidelines, the recommendations of which were based mainly on expert opinion during the first year of life.[5] As evidence of benefits are weak, long-term use of PPIs raises safety concerns. Morever, indications and duration of PPIs therapy varied widely among centers as demonstrated by a recent survey on the GERD management of EA patients.[6]

Herein, we aimed to gather and review the results of available clinical studies, to evaluate evidence in the use of PPIs in pediatric patients with EA, with a special focus on benefits and risks during the first years of life.

What is Known

- Chronic gastroesophageal reflux disease (GERD) is the most frequent problem in esophageal atresia pediatric patients.
- Proton pump inhibitors (PPIs) are commonly prescribed in this special condition.
- The question of prophylactic use and the efficacy of PPIs on GERD and other esophageal atresia complications is still debated.

What is New

- PPIs improve peptic esophagitis.
- PPIs do not assure effective prevention or treatment of anastomotic stricture, Barrett's esophagus, or respiratory complications in esophageal atresia pediatric patients, nor prevent antireflux surgery.
- Their side effects are almost unknown.

2 | METHODS

A literature search was performed using PubMed, Cochrane, and EMBASE, following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[7] (Figure 1). Two reviewers (G. D. and F. G.) analyzed the papers independently. The following search definitions were used:

- EA: Congenital anomalies with an interruption in the continuity of the esophagus, with or without persistent communication with the trachea.
- Long gap EA (LGEA): Delayed esophageal repair (after age 1 month) due to the gap length (excluding patients in whom surgery was delayed for reasons other than gap length such as extreme prematurity and severe malformations).[8] Since the definition of the long gap is not consensual and was lacking in many papers of our literature review, we decided to take this rough definition of an anastomosis delay due to the length of the gap rather than the type of EA or measurement of the gap.
- GERD assessment: The consensual definition is suggestive clinical symptoms AND positive pH/impedance monitoring (MII-pHm) and/or peptic esophagitis at esogastroduodenal endoscopy [EGD]), and anatomopathology.[5] Since the literature did not systematically use this definition, we focused our analysis on peptic esophagitis which was defined as macroscopic and/or histological changes. We looked at any objective measurement of GERD: pHm and/or MII-pHm. We also looked at clinical symptoms suggestive of GERD (regurgitations, burns, dysphagia).
- Anastomotic strictures (AS): Symptomatic reduction of the diameter of the esophagus anastomosis,[5] assessed by EGD and/or barium study and clinical signs[5] where early AS was occurring within the first month after EA repair, recurrent AS was requiring ≥3 dilatations, and refractory was requiring ≥5 dilatations at maximal 4-week intervals.[9]
- Intestinal metaplasia (IM)/gastric metaplasia (GM): Extension of salmon-colored mucosa into the tubular esophagus extending ≥1 cm proximal to the gastroesophageal junction (GEJ) with anatomopathological confirmation of IM (replacement of esophageal squamous epithelium by intestinal epithelium containing goblet cells)[10] or GM (replacement of esophageal squamous epithelium intestinal

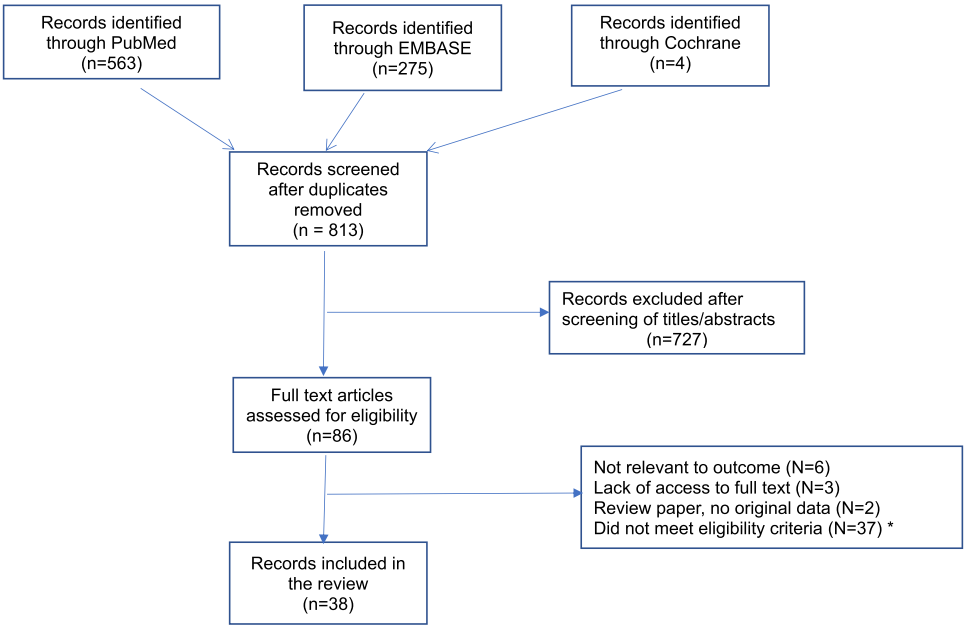


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart of study identification and selection.

by gastric fundic type epithelium [surface mucus, parietal, and chief cells], and/or gastric cardiac type epithelium [mucus-secreting cells]).[11]
- EoE: Clinicopathologic disorder of the esophagus, characterized by the association of upper gastrointestinal symptoms with esophageal mucosa containing at least 15 eosinophils per high-power field.[12]
- Respiratory morbidity: cough, dyspnea, asthma, tracheomalacia, or need for respiratory medication.[13]

2.1 | Inclusion criteria

We included articles published in English between 1980 and 2022 involving human participants for which articles were available in full-text format. Meta-analyses, systematic reviews, cohort studies, and case–control studies, including clear definitions of EA complications were included.

2.2 | Exclusion criteria

Gray literature, animal studies, studies with inaccessible full text, and studies published before 1980 were excluded.

2.3 | Search strategies

PubMed, EMBASE, and Cochrane were searched using keywords "esophagus atresia," "gastroesophageal reflux," "child," "newborn," "preschool," "school," "proton pump inhibitor" (including omeprazole, esomeprazole, lanzoprazole, pantoprazole, rabeprazole).

We defined five questions to be answered since they remain nonconsensual and practices vary widely among centers:

(1) What is the efficacy of PPIs in objective assessment of GERD, symptoms, and peptic esophagitis?
(2) Can PPIs substitute in some case cases for antireflux surgical procedure (ARP)?
(3) Are PPIs effective in preventing and treating AS?
(4) What is the efficacity of PPIs in preventing and treating of EoE, respiratory complications, and in LGEA?
(5) What are the adverse effects of PPIs?

2.4 | Statistical analysis

We conducted a meta-analysis of proportion on the two groups of studies: those with PPI use and those without PPI use.[14] We used the arcsine transformation to normalize the distributions of proportions.[15] The pooled proportion (with 95% confidence interval [CI]) was computed using a random effect model with the restricted maximum likelihood method. The heterogeneity of studies was assessed using the heterogeneity index I^2. The effect of PPI use on the difference in the pooled proportions was evaluated using a meta-regression with the PPI use (yes/no) as dependent variable. The results were presented using forest plots. The prevalence of esophageal histological

complications in EA were estimated using the same method without subgroup comparisons. Five published studies were comparative. Two studies compared the occurrence of acidic GERD according to the PPI use and three studies the occurrence of AS, all of them use odds ratio (OR) as effect sizes. We combined the results of these studies using meta-analysis of OR with fixed study effect. All statistical analyses were performed using the R software (version 4.2.3) with the packages meta and metafor and with the REVMAN software (Cochrane collaboration V5).

3 | RESULTS

We selected a total of 38 reports on the topic that met the criteria selection (Table S1), representing a cumulative 6044 patients with EA.[16–53] Fourteen studies were prospective and 24 were retrospective.

3.1 | Prevalence of GERD outcomes and related complications

Nine prospective and seven retrospective studies (representing 2318 patients) addressed the question of the frequency of esophageal histological complications in EA (Figure S1).[20,21,25,27,29,39,49,53–61] When confirmed by MII-pHm or esophageal biopsies, GERD is present among more than 25% of EA patients of all ages (Figure S2).[16,20–22,24,25,27,29,33,39,42,49,52–57,59–77] Figure S3 represents the pooled prevalence of GERD outcomes with 95% CI according to the different ages. Histological esophagitis prevalence is high in patients with EA [estimated pooled prevalence 54% (95% CI: 48%–60%)]; however, when considering only moderate and severe cases, this rate drops to 11% (95% CI: 5%–18%). IM remains rare (<1% [95% CI: 0%–1%]). To date, only 16 cases of pediatric IM have been reported (Figure S1D). The prevalence of GM [7% (95% CI: 2%–15%)] varies from 1.3% in infancy to 26% in adolescence. Less than 30% of GM disappeared with PPI treatment, while no case of IM regression was reported.

3.2 | PPI effects on esophagitis, acid/nonacid reflux, and symptoms

Evidence for the efficacy of PPIs for GERD and esophagitis is weak, due to a lack of well-designed studies, regarding both sample size and methodology (Table 1). The use of prophylactic PPIs (pPPIs) in the first year of life does not prevent objectively assessed GERD persistence at follow-up.[16–27] Two studies[16,21] including a comparative group shows a pooled OR of 0.75 (95% CI: 0.32; 1.74) (PPI vs. no PPI), $p = 0.50$ (Figure S4A). Although a significant rate of refractory esophagitis with PPIs is reported in patients with EA. PPI use improve peptic esophagitis in more than 50% of cases.[20,22,24,33,39,44,53] No robust evidence is available on PPI efficacy on other outcomes of GERD (i.e., MII-pHm and symptoms) in EA (Table 1).

3.3 | PPIs and ARP

Prophylactic use of PPIs during the first year of life was not associated with a significantly lower ARP rate at follow-up (Figure 2A,B): 18% (95% CI: 13%–24%) in PPI use group versus 19% (95% CI: 14%–24%) in no PPI use, $p = 0.82$ (comparison of pooled prevalence using test of meta-regression). Rate of LGEA [0.16 (95% CI: 0.12–0.21)] in the pPPI group was significantly higher ($p = 0.03$) than in "no PPI" group [0.10 (95% CI: 0.08–0.14)] (Figure 2C,D). Even after the exclusion of all LGEA cases (Figure 2E,F) PPI have not been shown to replace surgical fundoplication: ARP rate 3% (95% CI: 0.02%–8%) in PPI group versus 7% (95% CI:3%–14%) in no PPI group, $p = 0.12$.

3.4 | PPIs and AS

The differences in AS formation/recurrence rates in prophylactic versus nonprophylactic PPI users during the first year of life in patients who underwent surgery at birth for EA are shown on Figure 3A,B. The pooled prevalence of AS in the nine studies with PPI use was 41% (95% CI: 32%–49%) versus 35% (95% CI: 30%–40%) in the 24 studies with no PPI use. This difference did not reach statistical significance ($p = 0.23$; test of meta-regression), with same LGEA rate in both groups: pPPI: 0.11 (95% CI: 0.05; 0.17) versus "no pPPI" 0.11 (95% CI: 0.08–0.14), $p = 0.93$ (Figure 3C,D). Similarly, no effect of PPI was observed on rAS (subgroup pPPI: 0.21 (95% CI: 0.13; 0.30) vs. no PPI subgroup 0.18 (95% CI: 0.14; 0.23); $p = 0.63$) (Figure 3E,F).

When analyzing the three studies including a comparison group,[21,26,51] we neither could find any effects of PPI on AS (OR: 0.90; 95% CI: 0.60–1.37, $p = 0.64$ (Figure S4b).

3.5 | PPIs and EoE

Only one study[51] has addressed the relations between neonatal pPPI use and later EoE occurrence, demonstrating a positive association between PPI duration ($p = 0.018$) and cumulative dose ($p = 0.017$) with EoE development in EA. When EoE was associated with EA, PPIs alone induced remission in 50%–66%[25,43,50,53] of patients.

TABLE 1 PPI efficacity for GERD and GERD outcomes (esophagitis, acid reflux, symptoms) in patients with EA.

References	Study design	Aim	Population sample size	Intervention	Main findings	Main limitations
"Prophylactic PPIs" studies						
Caruso et al.[33]	Retrospective comparative	Effect of pPPIs during the first year of life	20 patients: – group 1:10 PPIs users – group 2: 10 matched "no-PPIs users"	Evaluation at 1 year: symptoms, EGD, MII-pHm Long-term outcome	1/Group 1 versus Group 2: – Less AS dilations: 50% vs. 90% ($p < 0.05$) – Better weight z score ($p < 0.05$)2/Long term in Group 2: more EoE, esophageal candidiasis, respiratory infections, and peptic E ($p < 0.05$)	Small sample size Not randomized Historical comparison
Flatrès et al.[22]	Prospective Longitudinal Single centre	Prevalence of GERD after pPPIs during the first year of life	70 patients	– Discontinuation of PPIs 5 days before pHm – Evaluation at 18 months: symptoms, pHm and/or EGD	pPPIs do not prevent GERD at 18 months, when prevalence remains high (64%)	Lack of consideration for esophageal histology Lack of control group
Tambucci et al.[49]	Retrospective	Analyze MII-pH, EGD and histology at 1 year	48 children on pPPIs Median age 1.2 year (1–1.3)	2 w after discontinuation of PPIs: – EGD with biopsies – MII-pHm	Despite pPPIs, symptoms (22% respiratory, 31% gastrointestinal), macroscopic E (8%), histological E (69%), and pathological esophageal acidity (25%) persist	
Lejeune et al.[24]	Prospective Multicenter	Risk factors associated with readmissions for respiratory causes in the first year in children with EA	1287 (88% on PPIs)	Prospective national register analysis	Despite pPPIs acidic GERD in 12% (pHm)	GERD defined as a positive pH test result and/or esophagitis on EGD
Allin et al.[16]	Prospective Multicenter International Comparative	Effect of pPPIs on AS formation in EA-TEF type C during first year of life	76 participants with EA (0 LGEA) analyzed at age 1 year – pPPIs group: 57 (H2b 73%, PPIs 16%) – No-pPPIs group: 19	Logistic regression analysis	Despite pPPIs and H2b, 51%[29] developed GERD versus 57%[11] in the "no-pPPIs" group	Most patients were on H2b GERD defined either on clinical grounds, or as evidenced by pHm or radiological investigation
"Prophylactic and Curative PPIs" studies						
Donoso et al.[21]	Prospective Single centre Cross-sectional	Predictors of histological esophagitis	65 patients with EA: – 47 children (median age 1.19 years); 75% on pPPIs during first year	In both groups: – Discontinuation of PPIs 4 weeks before evaluation	1/Despite PPIs: no significant difference ($p > 0.05$) in GERD complications (endoscopic E,	Lack of MII measures

(Continues)

TABLE 1 (Continued)

References	Study design	Aim	Population sample size	Intervention	Main findings	Main limitations
			– 18 adolescents (median age 15.17 years); 30% on PPIs	– Symptoms assessment – pHm and EGD with biopsies	histopathological E, acid reflux, and symptoms) between groups 2/GERD and E remain frequent after discontinuation of PPIs	
Yasuda et al.[29]	Prospective Cross-sectional	Evaluate whether CYP2C19 metabolizer phenotype contributes to refractory PPIs, nonallergic E in EA	314 participants with peptic E, all on PPIs: – 188 EA E, median age 2.6 y (1.2–6) – 126 non-EA E, median age 9 years[5–14]	– No discontinuation of PPIs before evaluation – Genotype for CYP2C19 polymorphism from esophageal biopsy samples – EGD with biopsies	Despite PPIs: – Refractory erosive E is 6.9% in EA vs. 0% in controls ($p < 0.001$) – Histological E in EA is 17% vs. 7.8% in controls ($p = 0.059$)	Control group is three times older Histological assessment based on Eosinophilic infiltration
Yasuda et al.[53]	Retrospective Single center	Efficacy of pPPIs on histological E	310 participants with EA (87% on PPIs) – Median age 3.7 years (1.8–6.5)	– No discontinuation of PPIs before evaluation – EGD with biopsies of patients on antiacids	– PPI therapy associated with reduced odds of abnormal esophageal biopsies ($p = 0.011$ for PPIs) – Despite pPPIs, erosive E present in 8.7% ($p = 0.059$) – Despite pPPIs, 50% of patients had histological E	High prevalence of LGEA (33%) Histological assessment based on Eosinophilic infiltration
Schneider et al.[27]	Prospective Multicenter International	– Prevalence of Barrett's esophagus (GM and/or IM) in adolescents with EA – Factors associated with BE	120 participants (28% on PPIs) – mean age 16.5 years (±1.4 years)	EGD with multistage esophageal biopsies ($N = 12$)	– Prevalence of BE 43%[51]: 42%[50] GM, 1%[1] IM – pPPIs and PPIs have no significant effect on BE by multivariate analysis	
Koivusalo et al.[39]	Retrospective	Assess esophageal histopathology in EA (E, GM, IM) at 1, 3, 5, 10, 15, and >15 years	209 EA participants with EA	Retrospective analysis of symptoms, esophageal histology, effects of anti-acids (PPIs or H2b)	21 out of 23 subjects (91%) improved histological E (grades II–III to grades 0–I) on antiacids	

TABLE 1 (Continued)

References	Study design	Aim	Population sample size	Intervention	Main findings	Main limitations
"Curative PPIs" studies						
Burjonrappa et al.[20]	Prospective	Incidence of GM/IM, efficacy of pHm in diagnosing acid GERD and period between the development of GERD and GM/IM	51 participants with EA – mean age: 6.6 years (7 months–19 years) – All on PPIs during the first year	Retrospective analysis – EGD: 38 participants – pHm: 33 participants	– Despite optimal PPI therapy, incidences of GM are 28% (11/38) and IM 2%[1] – Despite PPI therapy, BE regression of BE only 8% (1/12) of BE	Reflux index is considered pathological when >4.2%
Pashankar et al.[44]	Retrospective	Assess PPIs in ARP failure	18 patients: – 10 EA, 6 neurological impairment, 2 "normal" – ARP at median age 1.9 years (0.4–5.8 years) – Histological E in all	PPIs in all	– Clinical success on symptoms in 6/10 EA – Histological improvement of E in all	Very small sample size 2/10 EA lost to follow-up

Abbreviations: AS, anastomotic strictures; BE, Barrett's esophagus; E, esophagitis; EA, esophageal atresia; EGD, esogastroduodenal endoscopy; EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; GM, gastric metaplasia; H2b, H2-blockers; IM, intestinal metaplasia; LGEA, long gap EA; MII-pHm, pH/impedance monitoring; pPPI, prophylactic proton pump inhibitor.

3.6 | Respiratory morbidity and PPIs

Several retrospective studies (representing a cumulative 980 participants) have demonstrated a significant association between GERD and pulmonary complications (e.g., wheezing, respiratory exacerbations), although they used a heterogenous definition of GERD.[62,66,100–104] In contrast, other studies (representing 1554 participants), including two prospective,[24,105] did not show any significant association.[24,42,46,69,96,105] Only one prospective comparative study[26] and another retrospective study[46] showed that pPPIs improved neither tracheomalacia nor respiratory symptoms.[26]

3.7 | LGEA and PPIs

These include a high prevalence of GERD (66%–100%),[8,37,106,107] 45% rate of esophagitis,[8] 13% rate of Barrett's esophagus,[76] a high frequency of ARP (31%–65%),[8,37,106,107] and a high prevalence of AS (57%–79%).[8,37,76,93] These high-risk patients generally receive long-term PPI treatments.[106] However, due to the heterogeneity of treatment in this rare form of EA, almost no data exist on PPI efficacy; a single retrospective study reported GERD symptom improvement in 69% of cases.[37]

3.8 | Adverse events of PPIs in EA

Reported long-term suspected side effects have included an increased prevalence of EoE, depending on duration and cumulative dose[29,51] and increased *Clostridium difficile* infection was shown in one retrospective study of 92 participants[52] (3% vs. 0.036% in the general pediatric population). Bone mineral density decrease was not found in only one prospective study of 17 participants.[28]

4 | DISCUSSION

This comprehensive meta-analysis contributes a novel perspective on the controversial use of PPIs in pediatric EA.

GERD in patients with EA is thought to be related to a shorter intra-abdominal esophagus, dysmotility, larger hiatus, anatomical changes, and GEJ displacement with surgery due to traction of the distal esophagus, and retarded gastric emptying; several genes and biochemical pathways are also involved.[1] This condition appears more frequently than in the general population.[3,107] Although the prevalence of acid GERD at birth remains unknown, it appears to persist across infancy, childhood, and adolescence,

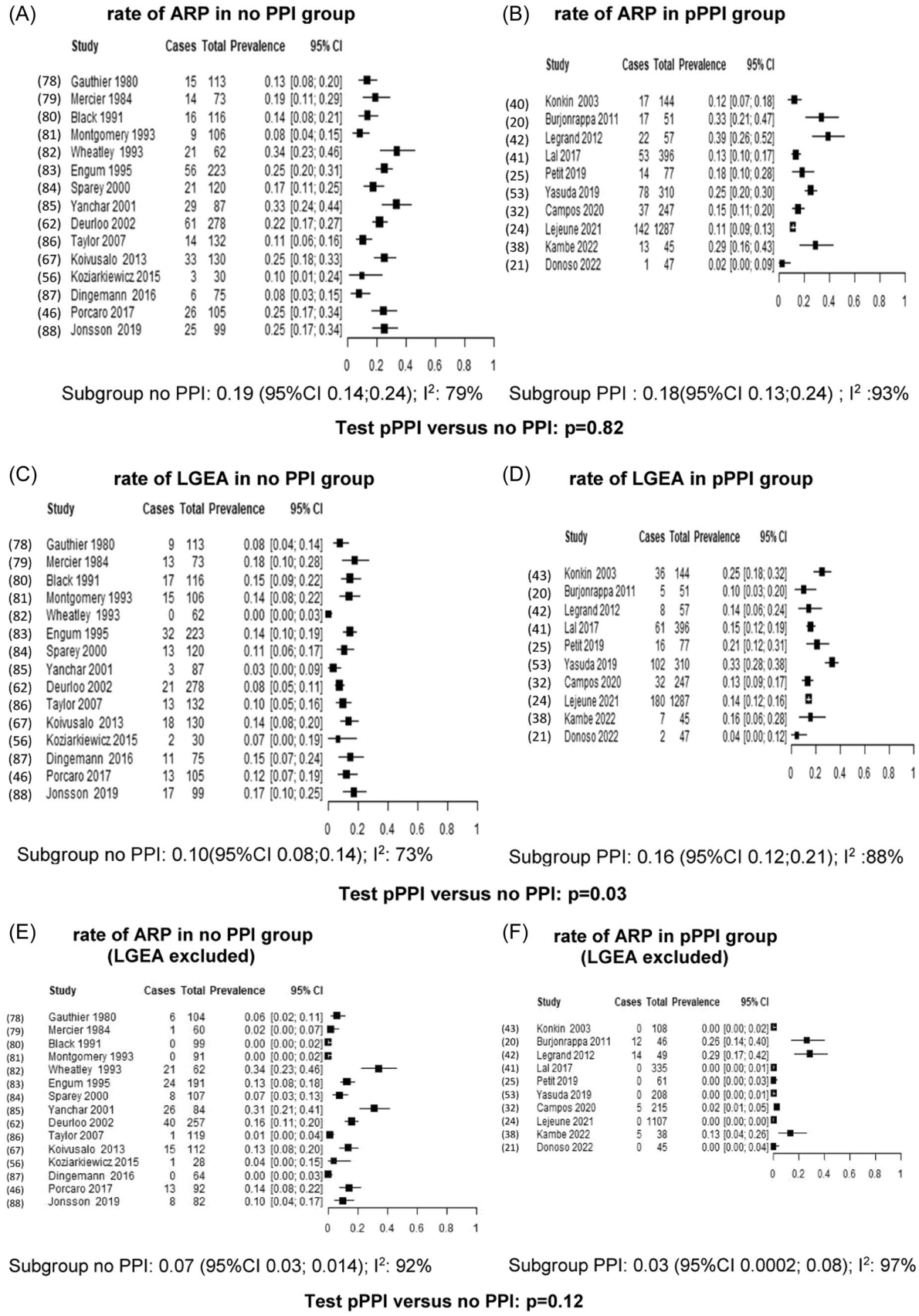


FIGURE 2 Rate of antireflux surgical procedures (ARP) and long gap esophageal atresia (LGEA) at any age according to prophylactic proton pump inhibitor (pPPI) use during the first year of life. (A) Rate of antireflux procedure in EA patient receiving no PPI. (B) Rate of antireflux procedure in EA patients receiving PPI. (C) Rate of long gap EA patients receiving no PPI. (D) Rate of long gap EA patients receiving PPI. (E) Rate of antireflux surgery in EA patients excluding long gap receiving no PPI. (F) Rate of antireflux surgery in EA patients excluding long gap receiving PPI. CI, confidence interval. References:[20,21,24,25,32,38,40–43,46,53,56,62,67,78–88]

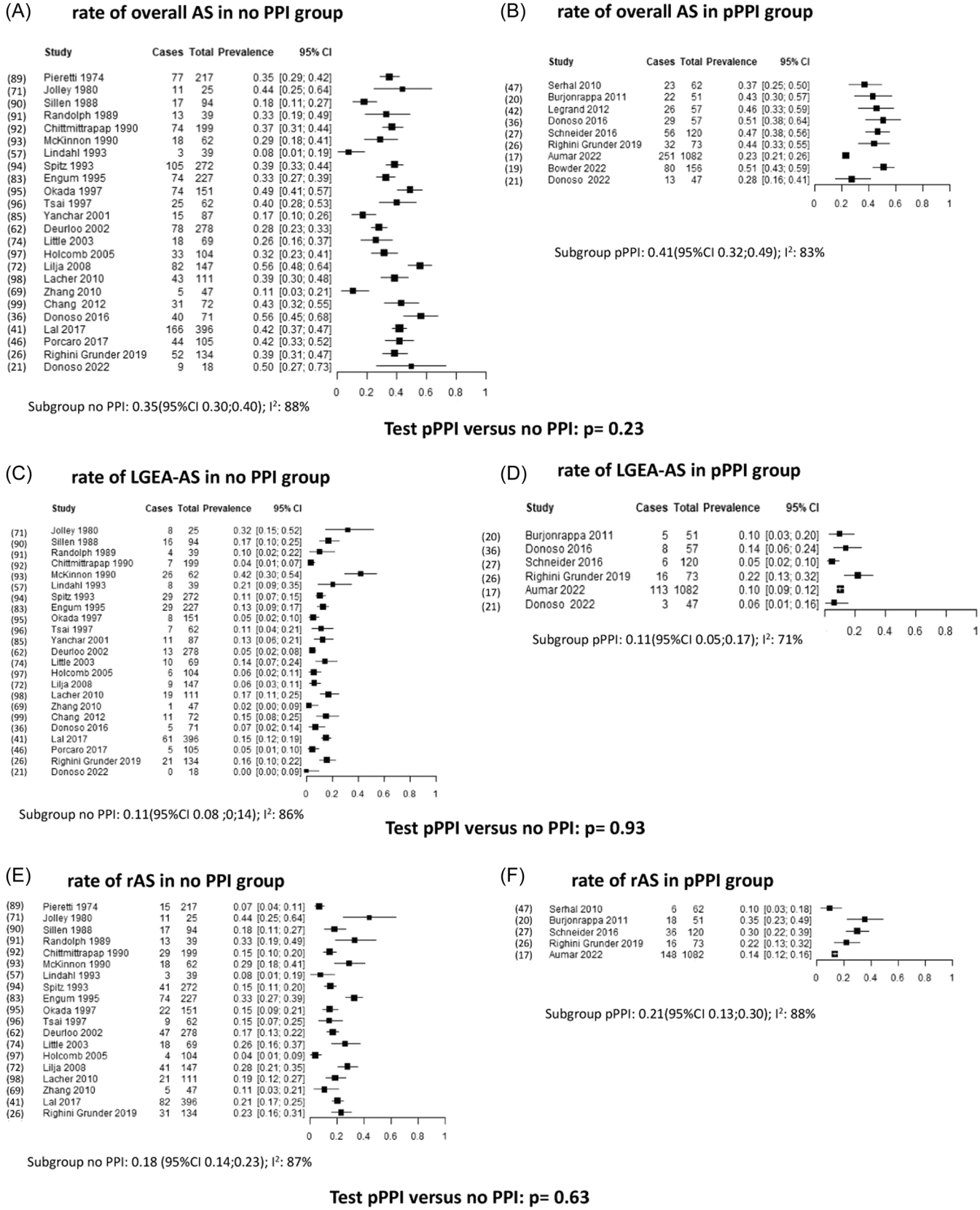


FIGURE 3 Proton pump inhibitor (PPI) effect on anastomotic stricture and on recurrent/refractory anastomotic stricture. (A) Rate of overall anastomotic strictures in EA patients receiving no PPI. (B) Rate of overall anastomotic strictures in EA patients receiving PPI. (C) Rate of long gap EA patients with anastomotic strictures receiving no PPI. (D) Rate of long gap EA patients with anastomotic strictures receiving PPI. (E) Rate of recurrent anastomotic strictures in EA patients receiving no PPI. (F) Rate of recurrent anastomotic strictures in EA patients receiving PPI. AS, anastomotic strictures; CI, confidence interval. References:[17,19–21,26,27,36,41,42,46,47,57,62,69,71,72,74,83,85,89–99]

affecting one-third to two-thirds of patients with EA (Figure S2). Pooled analyses of the cited studies confirm discordance between GERD symptoms, endoscopic esophagitis, histological esophagitis, and objective GERD measured by MII-pHm. Therefore, we intentionally focused on the most often available outcome: peptic esophagitis. Few authors used the complete definition of GERD or either defined in their papers as illustrated in Table 1, for example, MII-pHm measurement alone and/or esophageal histology but the clinical picture was often missing. The symptoms (when described) were not specific, biopsies number and localization varied, and MII-pHm measurements had different thresholds of positivity. These data suggest that PPIs provide good but incomplete control of peptic esophagitis. Histological esophagitis is half as prevalent in patients with EA who take PPIs[29,39] compared with those who do not. The mild/inconsistent efficacy of PPIs in EA compared with its effects in the general pediatric population could be due to nonacid reflux,[64,108,109] esophageal dysmotility,[76,110,111] inherent biological vulnerability of the esophageal mucosa to acid in EA,[1,112] presence of partial gastric pull-up secreting acid, or poor compliance.[25] Only one retrospective comparative small-sample study has directly evaluated the ESPGHAN-NASPGHAN guidelines for systematic PPIs, concluding that their systematic use during the first year prevents esophageal, nutritional, and respiratory complications.[33]

These studies provide no evidence that PPIs allow regression of Barrett's esophagus (GM or IM) in EA. There is an overall very low prevalence of IM (almost 1%), and a total of 16 reported pediatric cases, all persistent despite PPIs. However, we speculate that the prevalence of Barrett's esophagus is underestimated because few biopsies are performed in most studies. It is commonly accepted that IM has malignancy potential[10] and that acid suppression in adults with IM reduces the risk of esophageal cancer.[113] On this basis, aggressive GERD treatment with PPI therapy is required in the case of IM.[58] GM is 10 times more frequent in pediatric EA than in the general population, but its outcome and cancer risk remain controversial.

Our meta-analysis did not show that pPPI use during the first year of life was associated with reduced ARP. Two small-sample, retrospective observational studies suggest that PPIs could be an alternative to repeated surgery in case of ARP failure.[44,114] However, as no randomized trial comparing fundoplication versus acid-suppressive medication has been conducted in patients with EA, we cannot deduct causation. One explanation may be the difference in therapeutic strategies across centers, with some more surgically prone (and, therefore, less likely to use PPIs), while others more conservatively use PPI treatments for severe GERD.

A main finding herein is the lack of a significant association between PPI use and AS formation confirmed by a recent meta-analysis of Wyllie et al.[115] Both acid and nonacid GERD may induce inflammation and promote AS in experimental conditions.[116] Nevertheless, GERD's role in AS formation in human EA remains controversial: some studies have shown a clear association,[54,85,89,92,100,117,118] while others have demonstrated a lack of association.[22,26,32,36,42,69,98] In addition, the influence of ARP on AS remains debated. Some authors have shown an association between AS formation and ARP[17,62,89,100] which was unconfirmed by others.[26,32,36] This suggests that esophageal acidity may not be responsible for AS formation or recurrence, which may instead be influenced by surgical or anatomical factors.[17] Indeed, anastomosis under tension and delayed anastomosis probably induce ischemic changes, leading to abnormal healing and stenosis.[17] Despite the lack of randomized study, these data support hypothesis that PPIs do not prevent[16,19,26,30,32,36,47,119] nor treat AS[30,32,36] and AS recurrence.[30,32]

Recent reports[3,23,25,35,120] show that EoE occurs significantly more frequently in patients with EA than in either the general pediatric population or children with GERD symptoms refractory to antireflux treatment. EoE in pediatric patients with EA (EoE+EA+) is usually diagnosed between ages 1.5 and 6.6 years and is >200 times more prevalent (i.e., 9.5%–30%[23,25,35,45,50,53,119]) than in the general pediatric population (0.89–4/10,000).[121] In their study of outcomes after PPI treatment with topical steroids or the seven-foods exclusion diet in patients who were EoE+EA+, Chan et al.[122] reported an improvement in EoE after a median follow-up of 23 months: significant reduction in the intraepithelial eosinophil count, dysphagia, reflux symptoms, stricture prevalence, and need for dilations in both treatment options. PPIs can have disadvantages, including precipitating EoE onset in patients with EA who are exposed to PPIs from birth. Acid suppression in the esophagus may induce immunoglobulin E-mediated food allergies,[123] influence pH-protein digestion by pepsin, antigen recognition by immune cells, and alter the mucosal barrier, especially in long-term PPI therapy.[123] Using a transcriptome study with 94-gene mRNA expression signatures of EoE on esophageal biopsy specimens, Krishnan et al. demonstrated biological susceptibility to develop EoE in EA: 25% of those genes were dysregulated in EA+EoE– compared with EA–EoE–, including those involved with epithelial barrier function and inflammation.[120] One explanation for this association may be esophageal dysmotility and prolonged contact between food and mucosa.[119] In contrast, according to the general clinical recommendations for EoE management,[12] PPIs are a first-line treatment responsible for 54% of clinical and histologic responses. Possible explanations for this efficacy include an anti-inflammatory effect,[124] inhibition of eotaxin-3 expression (and, therefore, reduction of

eosinophil recruitment),[125] antioxidant properties,[126] and simple reduction of gastric acid reflux. Thus, current recommendations for EoE treatment in the general population should be applied in patients with EA, including PPIs.

One surprising finding of our review is that although EA pediatric patients receive long-term PPI treatment, data regarding tolerance is scarce. A structured follow-up is usually well-organized according to consensus guidelines,[5] could facilitate long-term assessment of PPI tolerance. Prospective long-term multicenter studies are needed to help answer these important questions about the benefits and risks of PPI use in patients with EA.

Our study was not without limitations. Although we selected trials and reports according to evidence-based criteria, they used different definitions, especially concerning GERD, AS, LGEA, and anastomotic tension. For example, the reflux index threshold used to define GERD was in the range of 4%–10% within these papers, and periods of PPI discontinuation before pHm varied from 5 days to 4 weeks. Clinical trials and reports were also biased by factors including small sample size, mixing samples of patients with and without LGEA, retrospective analyses, absence of information about anastomotic tension, variable numbers of esophageal biopsies, PPI doses varying in the range of 1–2 mg/kg/day within the same trial, and unreported doses. Treatment adherence to PPIs is rarely questioned, as are administration difficulties. This strongly suggests the need for consistent global definitions and prospective, controlled, register-based, or international trials with precise MII-pH definitions of GERD and consistent numbers of biopsies.

4.1 | Conclusion

Our review shows that PPI use in EA improves peptic esophagitis but limited data on other outcomes (symptoms, acid/nonacid reflux measured by MII-pHm). Available literature does not show effective prevention or treatment of AS, Barrett's esophagus, respiratory complications, or decrease of antireflux surgery. Esophageal dysmotility seems to have an important role in short- and long-term EA complications and is likely responsible for numerous PPI refractory symptoms. The side effects of PPIs in EA are almost unknown. Multicentric prospective studies are needed to guide the clinical choice of optimal treatment strategies for these patients.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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