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Review Article

Prophylactic Acid-suppression Medication to Prevent Anastomotic Strictures After Oesophageal Atresia Surgery: A Systematic Review and Meta-analysis

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ABSTRACT

Background: Anastomotic stricture is a common postoperative complication of oesophageal atresia ± tracheoesophageal fistula (OA/TOF) repair. Acid gastro-oesophageal reflux disease (GORD) is considered to be a factor in stricture formation and acid suppression medication is recommended post-operatively in consensus guidance. We aimed to investigate whether patients who were treated prophylactically with acid suppression medication had a reduced incidence of strictures compared to those who did not receive it.

Methods: A systematic review of studies was performed, searching multiple databases without language or date restrictions. Multiple reviewers independently assessed study eligibility and literature quality. The primary outcome was anastomotic stricture formation, with secondary outcomes of GORD, anastomotic leak, and oesophagitis. Meta-analysis was performed using a random effects model, and the results were expressed as an odds ratio (OR) with 95% confidence intervals (CI).

Results: No randomised studies on the topic were identified. Twelve observational studies were included in the analysis with ten reporting the primary outcome. The quality assessment showed a high risk of bias in several papers, predominantly due to non-objective methods of assessment of oesophageal stricture and the non-prospective, non-randomised nature of the studies. Overall, 1395 patients were evaluated, of which 753 received acid suppression medication. Meta-analysis revealed a trend towards increased odds of anastomotic strictures in infants receiving prophylactic medication, but this was not statistically significant (OR 1.33; 95% CI 0.92, 1.92). No significant differences were found in secondary outcomes.

Conclusions: This meta-analysis found no evidence of a statistically significant link between the prophylactic prescribing of acid suppression medication and the risk of developing anastomotic stricture after OA repair. The literature in this area is limited to observational studies and a randomised controlled trial is recommended to explore this question.

Level of Evidence: Level III.

1. Introduction

Oesophageal atresia (OA) with or without tracheoesophageal fistula (TOF), abbreviated to OA/TOF, is a congenital abnormality seen in 1 in 3000–5000 births [1]. The primary management of the condition is surgical repair of the defect [2] involving ligation of the TOF and anastomosis of the OA.

Anastomotic stricture is a common postoperative complication of OA/TOF surgery, up to 54% of patients were found to develop a stricture post-operatively in a large centre review of cases over a two-decade period [3]. The formation of an anastomotic stricture may occur as early as 30 days post-operatively or present many years following repair [4]. The pathogenesis of stricture formation is complex and multifactorial. The underlying mechanisms of stricture formation may include anastomosis under tension, two-

Abbreviations: OA/TOF, oesophageal atresia/tracheoesophageal fistula; GORD, gastro-oesophageal reflux disease; PPI, proton pump inhibitor; OR, odds ratio; CI, confidence interval; NEC, necrotising enterocolitis.

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layer anastomosis, excessive mobilisation of the oesophageal ends resulting in an ischaemic anastomosis, anastomotic leak, eosinophilic esophagitis, and gastro-oesophageal reflux disease [4–7]. Long oesophageal gap length and the consequent anastomotic tension with ischaemia post-repair increase the risk of stricture formation [7]. A meta-analysis of four retrospective studies also showed a significantly increased risk of stricture when a trans-anastomotic feeding tube was used post-operatively [8], although this is likely to be a surrogate for other confounding factors. The interplay of many of these factors may co-exist within the same patient leading to a requirement for repeated dilatations and long-term follow-up for symptomatic assessment. There is currently no widely validated prognostic tool for risk stratification of patients post-repair.

The presence of gastro-oesophageal reflux disease (GORD) has been reported as a key causal factor in the development of anastomotic strictures and anti-reflux surgery occurs in up to 20% of patients with oesophageal atresia [9]. The development of oesophagitis due to GORD in a dysmotile oesophagus with an anastomosis may cause an acute inflammatory response with localised fibrosis leading to stricture formation. Due to the potential link between GORD and the development of anastomotic strictures, the ESPGHAN-NASPGHAN expert consensus guidelines 2016 [10] recommended all patients be prescribed prophylactic acid suppression therapy after surgical repair in the form of a proton pump inhibitor (PPI).

However, there are several concerns regarding the routine use of acid suppression therapy. Although PPIs are known to increase gastric pH, the evidence regarding symptomatic relief in infants and children with GORD remains equivocal [11,12]. In preterm and low birth weight infants, acid suppression therapy has been linked to dysbiosis resulting in an increase in necrotising enterocolitis (NEC) [13,14] and increased neonatal infection [15,16]. Thus, the efficacy and safety of this therapy need to be comprehensively established.

This systematic review and meta-analysis examined the effect of prophylactic acid suppression treatment (H2 receptor antagonists or PPIs) on the development of anastomotic strictures post-surgery in infants with OA/TOF. Where data were available showing the effect of acid suppression on anastomotic leak, GORD, or oesophagitis these were also analysed.

2. Methods

2.1. Objectives

A systematic review and meta-analysis, using methods from the Cochrane Collaboration, to assess the efficacy and safety of using prophylactic acid-suppression medication in newborn infants after anastomotic surgery for OA/TOF to reduce the incidence of anastomotic strictures when compared with no/symptomatic use of acid suppression medication.

2.2. Inclusion and exclusion criteria

Randomised, quasi-randomised or observational case–control studies involving newborn infants who had surgery for OA/TOF were eligible for inclusion in the review. Studies were included if participating infants received acid-suppression medication prophylactically (without any signs of GORD and/or to prevent complications) after surgery (experimental group) and were compared with infants who did not receive prophylactic medication (control group); studies should also have reported outcomes that were relevant to the review (outlined below). Studies without a control group, or where medication was solely used for clinical reasons (GORD) were excluded from the analysis (Table 2).

2.3. Search strategy

We developed a search strategy using keywords and medical subject heading (MESH) terms for infant/newborn and preterm infants (combined with "OR"), anti-reflux medication including PPI and H2-blockers (combined with "OR") and OA/TOF. These were subsequently combined using the Boolean term "AND". Full details of the search strategy and results are presented in the supplementary information, which was conducted on multiple databases: EMBASE (1947-Present), Health Management Information Consortium (1979 to November 2022), MEDLINE ALL (1946 to February 22, 2023), APA PsycInfo (1806 to February Week 2 2023), CAB Abstracts (1910–2023 Week 07), Global Health (1910–2023 Week 07). The databases were searched in April 2022 and were re-run in February 2023. The search included papers in all languages, from all countries. All abstracts from the initial search were screened by two authors independently. A full-text review was undertaken for all articles meeting the inclusion criteria. References of included studies were also screened manually for inclusion.

2.4. Outcomes

The primary outcome was the incidence of anastomotic strictures, at least up to a year of age. Data on the following secondary outcomes were collected.

- Incidence of gastro-oesophageal reflux (as defined by the study authors)
- Incidence of anastomotic leak
- Incidence of oesophagitis/oesophageal erosion

2.5. Data collection

Data were collected on characteristics of studies and planned outcomes using a standardised data collection form (Supplementary Table 1) independently by two authors and then cross-checked for accuracy.

2.6. Statistical analysis

(1) Measurement of Treatment Effect

Statistical analysis was conducted using Review Manager (RevMan) version 5.4 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020). Only summary estimates are reported (no individual patient meta-analysis). For all categorical outcomes, data were extracted for each intervention group for analysis using the Mantel–Haenszel test and presented as odds ratios (ORs) with 95% confidence intervals (CI) and presented as forest plots. A random effects model was used for all analyses. For continuous outcomes, raw data on means and standard deviation (SD) were extracted for the pooled analysis, which is presented as mean difference (MD) with 95% CI. Significance was set at $p < 0.05$.

(2) Assessment of Bias in Included Studies

All studies included in the final analysis were assessed by two authors for risk of bias (low, high, or unknown) using the Risk Of Bias In Non-randomised Studies – of Exposure (ROBINS-E) tool [17]. For each domain, a judgement was made on the likely magnitude and direction of the bias and its likely impact on the outcomes.

Disagreements were resolved by consensus. A judgement was made on the overall risk of bias based on the above domains. Measurement of the primary outcome (oesophageal stricture) was considered a critical domain in the overall risk of bias analysis.

(3) Assessment of Heterogeneity

Heterogeneity was quantified using the Inaccuracy^2 (I^2) statistic and stratified as moderate ($I^2 < 50\%$) or substantial ($I^2 \geq 50\%$) (http://handbook.cochrane.org/). For observational studies, a random effects model was used.

2.7. Ethical approval

No specific ethical approval was required for this meta-analysis as all original studies had individual ethical approval. The review was prospectively registered on PROSPERO (CRD42022350592).

3. Results

A total of 159 records were returned by the systematic database search (Fig. 1) with one additional paper identified manually; after the removal of 18 duplicates, 142 unique records were screened for eligibility. Full-text papers from 22 studies were retrieved and 12 studies were included [16–27] in the final analysis (Table 1). All of the studies were observational in design; no randomised studies were identified in our search. The reasons for excluding the other 10 studies are recorded in Table 2 [18–27].

The assessment of the risk of bias in the included studies is presented in Supplementary Fig. 1. Of the ten studies that included data for the primary outcome, eight (80%) were assessed as having a high risk of bias for the assessment of oesophageal stricture due to non-objective methods of assessment. Thus, the overall risk of bias for these studies was also recorded as high. As all of the studies were observational in design, a random effects model was used for all analyses.

Demographics of the cohort including gestation at birth (preterm or term) & birthweight, and type of oesophageal atresia were infrequently reported in the papers and could not be pooled for the meta-analysis. The primary outcome was reported by ten studies involving 1395 infants [28–37]. There was no statistically significant difference in the rate of oesophageal stricture in the group of infants who received prophylactic acid suppression compared to infants who did not receive prophylactic acid suppression. There were more strictures observed in the prophylactic acid suppression group - pooled OR was increased to 1.33, although this did not reach statistical significance (95% CI 0.92, 1.92; Fig. 2). Due to the overall high risk of bias in eight studies, a sensitivity analysis was conducted by excluding them; the pooled results from the two remaining studies [30,34] were similar to the overall analysis (OR 1.27 [0.81, 1.97]). Secondary outcomes are presented in Supplementary Table 3 and Supplementary Fig. 2; no statistically significant differences were noted in the incidence of GORD (0.52 [0.24, 1.13]), anastomotic leak (0.84 [0.46, 1.55]) or oesophagitis/oesophageal erosion (1.16 [0.40, 3.38]) between the group of infants who received prophylactic acid suppression medication compared

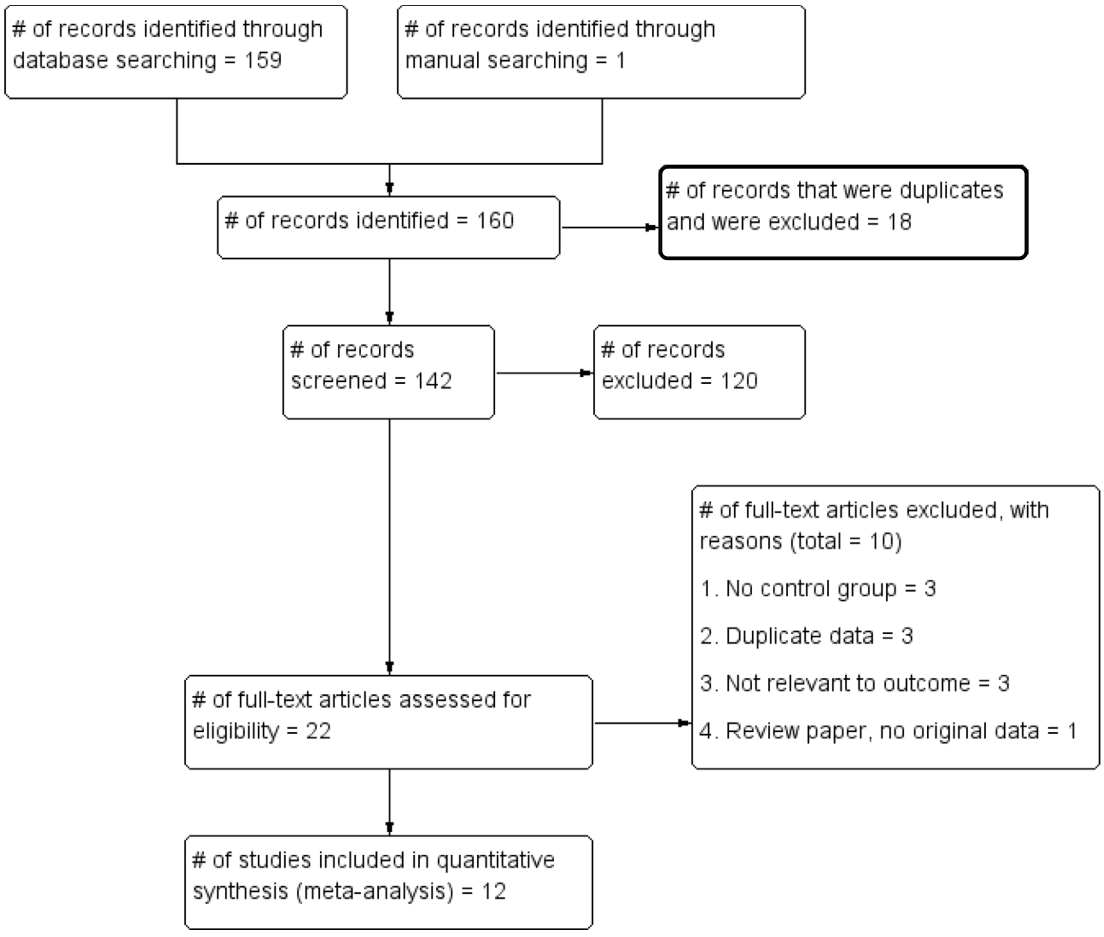

Fig. 1. PRISMA Flow diagram summarising the selection and exclusion criteria of published literature.

Table 1
Included studies.

Study ID	Inclusion & exclusion	Type of TOF included	Active treatment	Active treatment started	Standard treatment	Outcomes assessed	Stricture definition	Follow up duration	Comments
Allin 2014 [28]	Infants live born with TOF/OA in the UK & Ireland in 2008/9 *Exclusion:* Non-type C anomalies, incomplete follow-up information, death before 1 year	Type C only	Prophylactic antireflux medication (72% H2 antagonists, 16% PPI, 7% motility agents, 4% surface agents)	No time frame defined	No antireflux treatment	Mortality, stricture formation, anastomotic leak, and recurrent fistula formation	Undefined - different centres had different ways of diagnosing stricture formation.	1 year	Multicentre prospective.
Bowder 2022 [35]	Infants with type C anomaly treated between 2016 and 2020 in participating institutions. *Exclusion:* Non-type C anomalies, mortality before definitive repair, or definitive repair performed at a non-participating institution.	Type C only	Defined as PPI or H2 antagonist or both. No figures were given for each treatment	Postoperatively after the initial repair	No antireflux medication started by the point of initial discharge	Stricture formation	Presence of a symptomatic postoperative anastomotic narrowing requiring dilation.	1 year total	Multicentre prospective.
Caruso 2022 [37]	All children diagnosed with OA in a single centre 2016–2021	Undefined	PPI as per ESPGHAN-NASPGHAN 2016 guidelines	Postoperatively after the initial repair	PPI used symptomatically	Weight gain. The number of patients in both groups requiring endoscopic dilation of oesophageal stenosis was also reported - taken as stricture formation for this analysis	Endoscopic dilatation for oesophageal stenosis	1 year	Single centre retrospective Conference abstract lacks detail
Donoso 2017 [29]	Patients who underwent OA repair between 1994 & 2013 in a single unit	Undefined	Patients between 2005 and 2013 who were routinely prescribed PPIs as prophylaxis. 48 of 57 (84%) of this group received PPIs	Postoperatively after the initial repair	Patients born between 1994 and 2004 who were only prescribed PPIs symptomatically. 19 of 71 (27%) of this group received PPIs	Anastomotic stricture formation	Symptomatic narrowing of the oesophageal anastomosis requiring at least 1 balloon dilatation	5 years	Single centre retrospective
Grunder 2019 (2) [20]	Patients with OA systematically treated with PPI between 2005 & 2014	None excluded. The study cohort comprised Type C (88%), Type A (11%) & Type D (1%)	Oral PPI (lansoprazole 1 −2 mg/kg)	Initiated at the onset of oral or enteral feeding post-operatively after the initial repair	A historical cohort of 134 EA-TEF patients between 1990 and 2005, before the era of systematic PPI prescription	Primarily investigating factors associated with earlier discontinuation of PPI treatment. Also compared the stricture rate between the study group and a historical cohort.	The anastomotic stricture was defined as per expert guidance (Krishnan et al.). [10]	11 years	Single centre prospective, compared with a historic control group

(*continued on next page*)

Table 1 (*continued*)

Study ID	Inclusion & exclusion	Type of TOF included	Active treatment	Active treatment started	Standard treatment	Outcomes assessed	Stricture definition	Follow up duration	Comments
Hagander 2012 [46]	All patients with Type A or C TOF/OA who underwent repair and received prophylactic PPI *Exclusion:* Death pre or post-operatively (5), lost to follow-up (2) or did not receive PPI (3 − added to control cohort)	Type A or C	PPI (omeprazole/ esomeprazole 2 mg/kg once a day)	The first dose was given at the age of 3 days and then continued for at least 3 months and extended during the period of oesophageal dilatation	No prophylactic PPI	Stricture formation. Anastomotic leak was also reported	Routine X-ray 4 weeks post-op, if suspected stricture a procedure was done and either counted as a dilatation if balloon inflated or a calibration if not.	1 year after the last dilatation	Single centre, retrospective. These cohorts, both the treatment and control groups, are included in Stenstrom 2017 (1) [23]. Data was only taken from this paper for anastomotic leak, as this outcome is not reported in the latter study.
Jones 2020 [36]	All TOF/OA patients from 1994 to 2014 in a single centre *Exclusion:* cases that did not achieve oesophageal continuity at the initial surgical procedure, non-type C defects, cases with less than 1 year follow up	Type C only	Prophylactic antacid medication - not fully defined but all patients received ranitidine (H2 antagonist)	Within 48 h of primary repair	Not initially started on antacid medication, although some (44 of 98) were subsequently started on symptomatic treatment. This cohort was analysed separately from those who received no antacids.	Anastomotic stricture, number of dilatations	'Need for dilatation'. Unclear how this was assessed. The authors acknowledge this may have differed between cases due to variability between surgeons	1 year	Single centre, retrospective
Lal 2018 [31]	All patients between 2009 and 2014 in 11 centres with TOF/OA diagnosed within 30 days of life who underwent repair within the first 6 months of life	Type C only	Acid suppression with PPI (37%)/H2 receptor antagonist (39%) or both (24%)	Commenced in the postoperative period	No acid suppression	Anastomotic stricture, anastomotic leak	Presence of a symptomatic postoperative anastomotic narrowing requiring dilation.	1 year	Multi-centre, retrospective
LaRusso 2022 [32]	All patients with type C or D TOF/OA who underwent primary repair within the first six months of life during 25 years *Exclusion:* congenital oesophagal stenosis, operation at another facility, follow-up less than 12 months, major cardiac surgery during the same admission, death before 1 year of age, lack of a primary repair, and	Type C or D	Acid suppression with either H2 antagonist or PPI. No data was given on the proportions of each intervention.	Not stated, commenced by discharge	No acid suppression	Anastomotic stricture	The study used "an inclusive stricture definition that allowed us to include all patients judged clinically to have a stricture and confirmed with a contrast study or endoscopy"	1 year	Multi-centre, retrospective The primary focus of the paper was the use of trans anastomotic tubes and the characteristics of patients in the cohort who had strictures and did not. Data for acid suppression vs no acid suppression has been derived.

	insufficient data in the chart to evaluate the primary outcome.								
Murase 2015 [33]	Patients who underwent OA repair for type C TOF/OA between 2004 & 2013 in a single centre. *Exclusion:* patients followed up for <1 year	Type C only	Prophylactic H2 blocker (famotidine, 1 mg/kg/day)	Drug treatment commenced on the day of surgery and was continued for at least 6 months until an examination confirmed the absence of GER. All patients with GER continued treatment throughout the observation period (1 year after the primary repair).	Did not receive H2 blocker, otherwise same management	Anastomotic stricture	Stricture was diagnosed in patients who required balloon dilatation during contrast oesophagography. Oesophagography was routinely carried out and also if stricture was suspected.	1 year	Single centre, retrospective
Stenstrom 2017 (1) [23]	All patients with Type A or C TOF/OA who underwent repair and received prophylactic PPI *Exclusion:* Death pre or post-operatively (5), lost to follow-up (2) or did not receive PPI (3 − added to control cohort)	Type A or C	PPI continued for 3 months or 12 months and extended during the period of oesophageal dilatation	Commenced postoperatively	No prophylactic PPI	Anastomotic stricture	Narrowing of the oesophagus, identified on X-ray with contrast and verified by oesophagoscopy. Contrast esophagograms were routinely performed at 1−3, 6−8, and 12 months postoperatively, or following clinical suspicion of stricture formation (dysphagia, difficulty swallowing, and/or repeated vomiting)	Variable, range 1−16 years	Single centre, retrospective. Two cohorts received PPI, either for 3 months or 12 months so this cohort is heterogeneous
Yasuda 2019 [47]	OA patients at a single centre who underwent at least 1 upper endoscopy with biopsies between January 2016 and August 2018 *Exclusion:* H-type fistulas or isolated TOF	Type C (56%), Long gap (33%), Unknown (9%), Type A (<1%), Type D (<1%), Type B (<1%)	Acid suppression therapy (H2 blocker or PPI) as reported by caregiver interviews at the time of biopsy	Not stated	Patients were not on acid suppression therapy	Erosive and histologic esophagitis as found on biopsy	N/A	N/A Reports endoscopy results over 2.5 years	Single centre, retrospective

Table 2
Table of excluded studies with reasons.

Study ID	Reason for exclusion
Flatres 2022 [18]	No comparator/control group who did not receive PPI
Grunder 2018 [19]	Same data as Grunder 2019 (2) [20]
Grunder 2019 (1) [30]	Same data as Grunder 2019 (2) [20]
Lebreton 2017 [21]	No comparator/control group who did not receive PPI
Shawyer 2014 [22]	Review paper. References were examined for further papers, and no more were found than the original search.
Stenstrom 2017 (2) [34]	The same data as Stenstrom 2017 (1) [23] but does not include the comparator group who did not receive PPI
Tong 2016 [24]	No relevant data for the outcomes of interest
Tsai 2021 [25]	No relevant data for the outcomes of interest
Van Biervliet 2001 [26]	Case series, no comparator/control group who did not receive PPI
Vergouwe 2019 [27]	No relevant data for the outcomes of interest

with the group who either didn't receive it or only received symptomatic acid suppression.

4. Discussion

We have conducted a meta-analysis of observational studies using prophylactic acid-suppression medication for the prevention of oesophageal strictures after OA/TOF surgery in neonates. Our results show an increased incidence of strictures in infants who received prophylactic acid-suppression medication, although this was not statistically significant. Our findings and conclusions are in keeping with a previous systematic review that included four of the twelve papers identified by us [38]. However, due to the observational nature of the data and the non-objective assessment methods of the primary outcome in most of the studies, the evidence must be considered of low quality requiring urgent confirmation in an adequately powered randomised controlled trial.

PPIs bind irreversibly to the 'proton pump' (H^+-K^+-ATPase complex) of gastric parietal cells, inhibiting the ability of the cells to produce hydrochloric acid [39]. They have been shown to maintain intragastric pH > 4 for prolonged periods and seem to be superior to H2 receptor antagonists in healing erosive oesophagitis in adults [40]. Despite the demonstrated effectiveness of PPIs in increasing gastric pH, there is equivocal evidence with regard to the relief of symptoms in infants and children with GORD [11,12]. H2 receptor antagonists including ranitidine and famotidine have also been used postoperatively for OA/TOF patients, however, concerns regarding product safety due to a contaminant led to the withdrawal of ranitidine products from the market in 2019 [41].

There are concerns that gastric acid suppression may be harmful due to the important role of stomach acidity in the gastrointestinal tract host defence as a barrier to harmful pathogens [42]. Acid suppression therapy in low birth-weight infants has been linked to an increase in necrotising enterocolitis (NEC) [13,14] and increased neonatal infection [15,16]. PPI use has been demonstrated to increase the risk of developing *C. difficile* infection in paediatric patients with long-term use [43]. Given these potential risks of long-term treatment, the practice of prophylactically prescribing prophylactic PPIs in this population should be scrutinised to demonstrate objective benefits.

The main strength of this work is the extensive and systematic search for potential studies and the identification of multiple papers which have not been included in a meta-analysis previously. However, all the identified studies were observational, many with historical controls. This raises a serious risk of bias in all the studies and the published data. Specifically, the method of diagnosing an anastomotic stricture was non-objective in most of the studies, further reducing the reliability and validity of the data. The anatomical type of OA/TOF (Type A-E) was inconsistently reported in the papers. As Type A atresias may have a higher incidence of strictures [44], it is important to know the anatomical variant so that the comparison can be matched. Demographic data has been inconsistently reported in the studies and was not interpretable for meta-analysis in the studies which did publish demographics. As prematurity can have an impact on surgical complications, demographics is an important point to consider for future studies. Many of the studies had historical controls; change in practice between epochs, especially if the diagnosis of the outcome is based on subjective considerations, could potentially have a substantive effect on the published data and its interpretation.

Currently, available data and our meta-analysis does not support the prophylactic use of acid suppression medication after anastomotic surgery for OA/TOF for the prevention of strictures. As this remains an important topic for patients with OA/TOF, an adequately powered randomised controlled trial is recommended to identify the objective benefits of using prophylactic acid suppression medication after OA/TOF surgery. The TOAST (Treating Oesophageal Atresia to Prevent Strictures) study, a multi-centre randomised trial [45], is being set up in the UK with an aim to answer the question "Should babies born with oesophageal atresia all be treated routinely with antacid medication to reduce strictures?" (https://www.npeu.ox.ac.uk/toast/clinicians). As identified as part of our work, special attention must be paid to agree on a unified definition of strictures and how they are diagnosed prior to the initiation of the study. In addition, background demographic data, use of trans anastomotic feeding tubes, medication details including doses, types of atresias included in the study and important safety data on

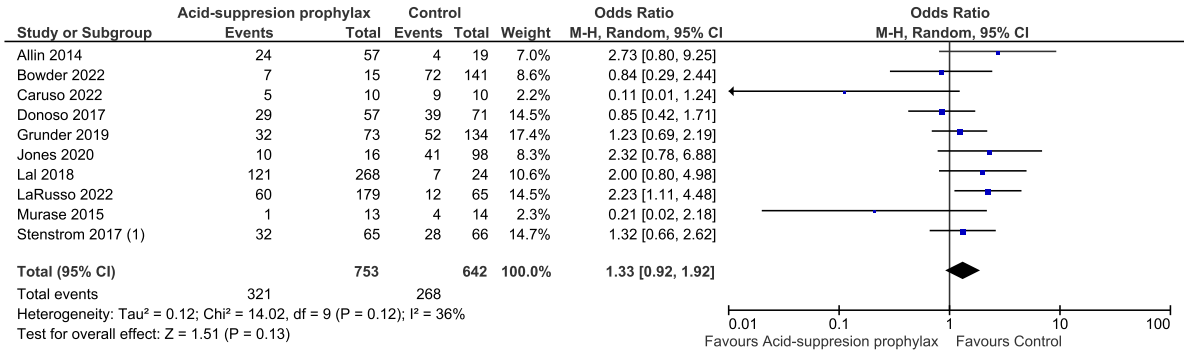

Fig. 2. Forest plot of the primary outcome.

the effect of medication must also be collected to allow a comprehensive assessment of this practice.

Conflicts of interest

The authors declare no relevant conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpedsurg.2023.05.024.

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