Anti-reflux mucosectomy for refractory gastroesophageal reflux disease: a systematic review and meta-analysis*

Authors
Rajat Garg**,1, Abdul Mohammed**,2, Amandeep Singh1, Mary Schleicher3, Prashanti N. Thota1, Tarun Rustagi4, Madhusudhan R Sanaka1

Institutions
1 Department of Gastroenterology, Hepatology and Nutrition, Digestive Diseases and Surgery Institute; Cleveland Clinic, Cleveland, Ohio, United States
2 Department of Internal Medicine, Cleveland Clinic, Cleveland, Ohio, United States
3 Cleveland Clinic Alumni library, Cleveland Clinic, Cleveland, Ohio, United States
4 Department of Gastroenterology and Hepatology, University of New Mexico, Albuquerque, New Mexico, United States

submitted 23.8.2021
accepted after revision 15.11.2021

Bibliography
Endosc Int Open 2022; 10: E854–E864
DOI 10.1055/a-1802-0220
ISSN 2364-3722
© 2022. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (https://creativecommons.org/licenses/by-nc-nd/4.0/)

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Supplementary material is available under https://doi.org/10.1055/a-1802-0220

Corresponding author
Rajat Garg, MD, Department of Gastroenterology, Hepatology and Nutrition, 9500 Euclid Avenue, Cleveland Clinic Foundation, Cleveland, OH, USA - 44195
Fax: +1- 440-312-8588
drgargrajat@gmail.com

ABSTRACT

Background and study aims Anti-reflux mucosectomy (ARMS) is an emerging endoscopic treatment for refractory gastroesophageal reflux disease (GERD). We conducted a systematic review and meta-analysis to evaluate the safety and efficacy of ARMS in refractory GERD.

Methods A comprehensive search of multiple databases (through March 2020) was performed to identify studies that reported outcomes of ARMS for refractory GERD. Outcomes assessed included technical success, clinical response, and adverse events (AEs). Clinical response was defined as discontinuation (complete) or reduction (partial) of proton pump inhibitors post-ARMS at follow up.

Results A total of 307 patients (mean age 46.9 [8.1] years, 41.5 % females) were included from 10 studies. The technical success and clinical response rates were 97.7 % (95% confidence interval [CI], 94.6–99.0) and 80.1 % (95% CI, 61.6–91.0), respectively. The pooled rate of complete and partial clinical response was 65.3 % (95% CI, 51.4–77.0) and 21.5 % (95% CI, 14.2–31.2), respectively. The rate of AEs was 17.2 % (95% CI, 13.1–22.2) with most common AE being dysphagia/esophageal stricture followed by bleeding with rates of 11.4 % and 5.0 %, respectively. GERD health-related quality of life (GERD-HRQL) (mean difference [MD] = 14.9, P<0.001), GERD questionnaire (GERD-Q) (MD= 4.85, P<0.001) and mean acid exposure time (MD= 2.39, P=0.01) decreased significantly post-ARMS as compared to pre-procedure. There was no difference in terms of clinical response and AEs between ARMS and ARMS with banding on subgroup analysis.

Conclusions ARMS is a safe and effective procedure for treatment of refractory GERD with high rates of clinical response, acceptable safety profile and significant improvement in GERD-related quality of life. Prospective studies are needed to validate our findings.

* Meeting presentations: An abstract of this manuscript was accepted for poster presentation at the American College of Gastroenterology, 2021.

** These authors contributed equally.
Introduction
Gastroesophageal reflux disease (GERD) is a consequence of the failure of the normal anti-reflux barriers to protect against abnormal amounts of retrograde reflux of material from the stomach to the esophagus [1]. Longstanding GERD can predispose to esophagitis, esophageal ulcers, peptic esophageal strictures, Barrett’s esophagus, and adenocarcinoma of the esophagus. Proton pump inhibitors (PPIs) are first-line treatment for GERD. They are antacid medications that inhibit meal-stimulated and nocturnal acid secretion [2]. About 30% to 40% of patients with GERD are refractory to treatment with PPIs [3]. Increased frequency or volume of reflux, ineffective PPI-induced control of gastric secretion, esophageal hypersensitivity, bile content of gastric juice, and other co-existing conditions such as obesity, hiatal hernia, and Helicobacter pylori infection are risk factors for refractory GERD [3].

Anti-reflux surgery such as laparoscopic fundoplication is beneficial in patients with refractory GERD but 25% of patients have postoperative dysphagia, gas bloat syndrome, diarrhea, and increased flatus [4]. Moreover, 25% to 62% of patients require acid-suppressive medications 5 to 15 years after their anti-reflux surgery [5]. As a result, several novel surgical techniques that do not alter the anatomy of the cardia have been developed, but they, too, are associated with procedural limitations [6, 7]. A series of endoscopic treatments for treatment of GERD, such as transoral incisionless fundoplication (TIF) and magnetic sphincter augmentation (MSA), have also failed to show long-term efficacy [8]. As a result, the American Gastroenterological Association Institute, in their technical review on the use of endoscopic therapy for the treatment of GERD, reported that there were no definite indications for endoscopic therapy for GERD [9].

Anti-reflux mucosectomy (ARMS) is a new endoscopic technique for treatment of refractory GERD first reported by Inoue et al [10]. The aim of the procedure is to achieve fundoplication by submucosal fibrosis after mucosectomy at the esophagogastric junction (EGJ) and it has the advantage of an endoscopic approach. Since the introduction of ARMS, several prospective and retrospective studies have been performed to assess outcomes with it. We performed a systematic review and meta-analysis to assess the efficacy and safety of ARMS in treatment of refractory GERD.

Methods
Search strategy
We conducted a comprehensive search of several databases from inception to March 2021. The databases included Ovid MEDLINE and Epub Ahead of Print, In-Process and other non-indexed citations, Ovid Embase, Ovid Cochrane Central Register of Controlled trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. An experienced medical librarian using inputs from the study authors helped with the literature search. Controlled vocabulary supplemented with keywords was used to search for studies of interest. The full search strategy is available in Appendix 1. The MOOSE and PRISMA checklist were followed and are provided in Appendix 2 and Appendix 3 [11, 12].

Study selection
In this meta-analysis, we included studies that evaluated outcomes of ARMS in patients with refractory GERD. Studies were included irrespective of the study sample size, inpatient/outpatient setting, and geography as long as they provided data needed for the analysis.

Studies done in pediatric populations (age < 18 years), and studies not published in English were our only exclusion criteria. In case of multiple publications from the same cohort and/or overlapping cohorts, data from the most recent and/or most appropriate comprehensive report were retained.

Data abstraction and quality assessment
Data on study-related outcomes in the individual studies were abstracted in a standardized form by at least two authors (RG, AM), and two authors (RG, AM) did the quality scoring independently. Primary study authors were contacted via email as needed for further information and/or clarification on data.

The Newcastle-Ottawa scale for cohort studies was used to assess the quality of studies [13]. This quality score consisted of eight questions, the details of which are provided in Supplementary Table 1.

Outcomes assessed
1. Pooled rate of technical success.
2. Pooled rate of clinical success based on discontinuation or reduction of PPI after ARMS. It was further categorized into complete if patients were able to discontinue PPIs post-ARMS and partial if ARMS led to reduction in PPI dose.
3. Pooled rate of adverse events (AEs) after ARMS. It was further classified into dysphagia and bleeding after ARMS.
4. Symptomatic improvement was further measured by validated pre-procedure and post-procedure questionnaire to assess typical and atypical GERD symptoms: GERD-Health-Related Quality of Life (HRQL) and Gastroesophageal Reflux Disease Questionnaire (GERD-Q).
5. Pre-and Post-ARMS DeMeester score and mean acid exposure time (AET) was also measured based on 24-hour pH study.

Statistical analysis
We used meta-analysis techniques to calculate the pooled estimates in each case following the methods suggested by DerSimonian and Laird using the random-effects model [14]. When the incidence of an outcome was zero in a study, a continuity correction of 0.5 was added to the number of incident cases before statistical analysis [15]. Mean difference between pre-procedure and post-procedure measures were calculated by inverse variance method. We assessed heterogeneity between study-specific estimates by using Cochran Q statistical test for heterogeneity and the I² statistics [16]. In this, values of <30%, 30% to 60%, 61% to 75%, and >75% were suggestive of low, moderate, substantial, and considerable heterogeneity, respectively [17]. Publication bias was ascertained, qualitatively, by
visual inspection of funnel plot and quantitatively, by the Egger test [18]. P > 0.05 was used a priori to define significance of the difference between the groups compared as provided the statistical software. We conducted further subgroup analysis based on use of banding with ARMS.

The analysis was performed using Rstudio and Revman software.

Results

Search results and population characteristics

From an initial 909 studies, 560 records were screened, and 36 full-length articles were reviewed. Ten studies were included in the final analysis that reported outcomes of ARMS [19–28]. The schematic diagram of study selection is shown in Fig. 1.

A total of 307 patients with mean age 46.9 years (8.1) (range 37–56.8 years) were included in our study. Gender was reported in seven studies and among them, 41.5% of patients were female. In six studies, ARMS-endoscopic mucosal resection (EMR) was performed and four studies, ARMS with banding was performed. All patients were on maximal PPI therapy before ARMS. The mean procedure duration was 40.3 minutes (8.5) (range 31.2–54.7 minutes) reported in six studies. Patient characteristics and data on assessed outcomes are shown in Table 1.

Characteristics and quality of included studies

Eight studies were prospective and two were retrospective in nature. Of the 10 observational studies, four studies were high quality, five were medium and one was low quality. Quality assessment is shown in Supplementary Table 1.

Meta-analysis outcomes

Technical and clinical success

The pooled rate of immediate technical success was 97.7% (95% confidence interval [CI] 94.6–99.0, I² = 0%) (Fig. 2a). ARMS was performed most using EMR in six studies and four studies utilized banding device with ARMS. Sumi et al also performed seven cases of ARMS with endoscopic mucosal dissection (ESD) [26].

Follow-up time ranged from 1 to 12 months. The pooled rate of clinical success was 80.1% (95% CI, 61.6–91.0, I² = 84.9%) (Fig. 2b). Rates of complete and partial clinical success were 65.3% (95% CI, 51.4–77.0, I² = 73.1) and 21.5% (95% CI, 14.2–31.2, I² = 25.5), respectively (Fig. 2c and Fig. 2d).

Adverse events

The pooled rate of overall AEs was 17.2% (95% CI, 13.1–22.2, I² = 1.9%) (Fig. 3a). There were a total of 49 AEs. The most common AE was dysphagia from esophageal stricture (n = 32) followed by bleeding (n = 8), three cases of perforation, muscle injury, and aspiration pneumonia each. Pooled rates of dysphagia and bleeding were 11.4% (95% CI, 8.2–15.7, I² = 0) and 5% (95% CI, 1.9–12.3, I² = 51.3%), respectively (Fig. 3b and Fig. 3c).

Symptomatic improvement

Symptom improvement was measured by two validated GERD-associated scoring systems. Overall, mean GERD-HRQL (health-related quality of life) scores were reported in four studies, and they significantly improved after ARMS as compared to pre-procedure scores (mean difference [MD] = 14.9, [95% CI, 9.3–20.6], I² = 85%, P < 0.001). GERD-Q was reported in five studies and significantly improved after ARMS with MD of 4.85 [95% CI, 2.7–7.0, I² = 95%, P < 0.001]. These results are shown in Fig. 4a and Fig. 4b.

pH monitoring

Objective measures of GERD improvement were determined by esophageal pH monitoring. Three studies reported results of pre-ARMS and post-ARMS pH study. Mean AET (MD = 2.39, 95% CI, 0.47–4.3, I² = 74%, P = 0.01) decreased significantly post-ARMS as compared to pre-procedure (Fig. 4c). Post-procedure DeMeester score was also reported in three studies. The mean difference between post- and pre-ARMS DeMeester score was 36.02 (95% CI, −8.83 to 80.87, I² = 99, P = 0.12) (Fig. 4d).

Subgroup analysis

We performed subgroup analysis based on ARMS with banding (ARMS-B) and without banding. Among the 10 studies, six studies did not use banding with ARMS and four studies used ARMS-B. Compared to ARMS-B, ARMS did not have any statistical sig-
| Author, year | Technique | Age, mean years (SD) | Females | No. patients | GERD-HRQL score | GERD-Q score mean (SD) | DeMeester score mean (SD) | Mean esophageal acid exposure time (%) (SD) | Procedure time, mean, minutes (SD) | Technical success | Follow-up mean time (SD) | Clinical success | Partial clinical success | Complete clinical success | Adverse events | Dysphagia | Bleeding |
|--------------|-----------|----------------------|---------|-------------|----------------|------------------------|--------------------------|--------------------------------|--------------------------|----------------|------------------------|----------------|------------------------|----------------------|---------------|----------|---------|
| Bapaye et al, 2017 | ARMS | 40.8 (19.2) | 4 | 15 | 40.4 | 7.6 | NR | NR | 85.8 | 5.9 | NR | NR | 15 | 1 mo | 15 | 4 | 11 | 3 | 1 | 0 |
| Debourdeau et al, 2020 | ARMS-B | 44 (7.5) | 5 | 6 | 30.6 (7.7) | 6.8 (3.7) | 13.3 (1.1) | 6.2 (4.0) | NR | NR | NR | NR | <40 min | 6 | 3 mo | 3 | 2 | 1 | 2 | 1 | 1 |
| Wong et al, 2020 | ARMS-B | 55 (17) | 22 | 33 | 16.0 (12.0) (N = 24) | 6.0 (7.1) (N = 15) | NR | NR | 19.6 (10.1) | NR | NR | NR | 36 (13) | 33 | 6 mo | 30 | 0 | 30 | 5 | 3 | 1 |
| Kessler et al, 2013 | ARMS-B | NR | NR | 10 | 26.6 (0.4) | 9 (1.6) | NR | NR | NR | NR | 8.35 (0.04) (n = 9) | 5.8 (1.19) | NR | 10 | 6 mo | 10 | 0 | 10 | 3 | 3 | 0 |
| Prasad et al, 2019 | ARMS | 41 – 60 | NR | 11 | NR | NR | NR | NR | NR | NR | NR | NR | NR | 11 | 6 mo | 8 | 8 | 0 | 0 | 0 |
| Monino et al, 2020 | ARMS-B | 56.87 (14.47) | 10 | 21 | 25.6 (8.8) (N = 18) | 16.8 (6.4) | 12.5 (1.5) (n = 18) | 9 (2) (n = 18) | NR | NR | NR | NR | 35 (11) | 21 | 10 (5) mo | 16 | 4 | 12 | 4 | 3 | 1 |
| Ortega et al, 2019 | ARMS | 41 | NR | 7 | NR | NR | 19 | 3 | 37.1 | NR | NR | NR | 45 min | 7 | 3 mo | 4 | 4 | 3 | 0 | 3 |
| Author, year       | Technique | Age, mean years (SD) | Females | No. patients | GERD-HRQL score mean (SD) | GERD-Q score mean (SD) | DeMeester score mean (SD) | Mean esophageal acid exposure time (%) (SD) | Procedure time, mean, minutes (SD) | Technical success | Follow-up mean time (SD) | Clinical success | Partial clinical success | Complete clinical success | Adverse events | Dysphagia | Bleeding |
|-------------------|-----------|----------------------|---------|--------------|--------------------------|------------------------|-------------------------|---------------------------------|--------------------------------------|-----------------|-----------------------|------------------|-------------------------|------------------------|----------------|----------|---------|
| Patil et al, 2020 | ARMS      | 37 (9.9)             | 18      | 62           | NR                       | 10.6 (1.9)             | 3.4 (1.5)               | 76.8 (18.3)                     | 14.3 (6.1)                         | NR              | 62                    | 12 mo           | 55                      | 12                  | 43                      | 10                    | 5          | 0        |
| Sumi et al, 2020  | ARMS      | 54.0 (15.7)          | 46      | 109          | NR                       | 9.4 (2.7)              | 6.6 (2.5)               | 64.4 (75.7)                     | 24.9 (36.0)                        | 20.8 (24.3)       | 109                   | 2–6 mo          | 42                      | 42                  | 17                      | 14                    | 2          |
| Yoo et al, 2020   | ARMS      | 51.3 (16.3)          | 11      | 33           | NR                       | 11.1 (3.1)             | 6.8 (3.1)               | 14.3 (10.9)                     | 7.7 (9.4)                           | 3.1 (3.1)         | 33.5                  | 6 mo            | 31                      | 10                  | 21                      | 2                     | 2          |

ARMS, anti-reflux mucosectomy; GERD, gastroesophageal reflux disease; GERD-HRQL, GERD health-related quality of life; GERD-Q, GERD questionnaire; NR, not reported; SD, standard deviation.
### Study Cases Total Proportion 95% CI

| Study                  | Cases | Total | Proportion | 95% CI          |
|------------------------|-------|-------|------------|-----------------|
| Bapaye et al. 2017     | 15    | 15    | 1.000      | [0.650; 0.998]  |
| Debourdeau et al. 2020 | 6     | 6     | 1.000      | [0.423; 0.996]  |
| Wong et al. 2020       | 33    | 33    | 1.000      | [0.804; 0.999]  |
| Kessler et al. 2013    | 10    | 10    | 1.000      | [0.552; 0.997]  |
| Prasad et al. 2019     | 11    | 11    | 1.000      | [0.575; 0.997]  |
| Monino et al. 2020     | 21    | 21    | 1.000      | [0.723; 0.999]  |
| Ortega et al. 2019     | 7     | 7     | 1.000      | [0.461; 0.996]  |
| Patil et al. 2020      | 62    | 62    | 1.000      | [0.885; 1.000]  |
| Sumi et al. 2020       | 109   | 109   | 1.000      | [0.932; 1.000]  |
| Yoo et al. 2020        | 33    | 33    | 1.000      | [0.804; 0.999]  |
| **Random effects model** |   |       | **0.997** | **[0.946; 0.990]** |

**a**

### Study Cases Total Proportion 95% CI

| Study                  | Cases | Total | Proportion | 95% CI          |
|------------------------|-------|-------|------------|-----------------|
| Bapaye et al. 2017     | 11    | 15    | 0.733      | [0.467; 0.896]  |
| Debourdeau et al. 2020 | 1     | 6     | 0.167      | [0.023; 0.631]  |
| Wong et al. 2020       | 30    | 33    | 0.909      | [0.753; 0.970]  |
| Kessler et al. 2013    | 10    | 10    | 1.000      | [0.552; 0.997]  |
| Prasad et al. 2019     | 8     | 11    | 0.727      | [0.414; 0.910]  |
| Monino et al. 2020     | 16    | 21    | 0.762      | [0.540; 0.897]  |
| Ortega et al. 2019     | 4     | 7     | 0.571      | [0.230; 0.856]  |
| Patil et al. 2020      | 55    | 62    | 0.887      | [0.782; 0.945]  |
| Sumi et al. 2020       | 42    | 100   | 0.420      | [0.327; 0.519]  |
| Yoo et al. 2020        | 31    | 33    | 0.939      | [0.788; 0.985]  |
| **Random effects model** |   |       | **0.801** | **[0.616; 0.910]** |

**b**

### Study Cases Total Proportion 95% CI

| Study                  | Cases | Total | Proportion | 95% CI          |
|------------------------|-------|-------|------------|-----------------|
| Bapaye et al. 2017     | 4     | 15    | 0.267      | [0.104; 0.533]  |
| Debourdeau et al. 2020 | 2     | 6     | 0.333      | [0.084; 0.732]  |
| Wong et al. 2020       | 0     | 33    | 0.000      | [0.000; 0.196]  |
| Kessler et al. 2013    | 0     | 10    | 0.000      | [0.003; 0.448]  |
| Monino et al. 2020     | 4     | 21    | 0.190      | [0.073; 0.412]  |
| Patil et al. 2020      | 12    | 62    | 0.194      | [0.113; 0.311]  |
| Yoo et al. 2020        | 10    | 33    | 0.303      | [0.171; 0.477]  |
| **Random effects model** |   |       | **0.215** | **[0.142; 0.312]** |

**c**

### Fig. 2 Forest plots showing a pooled rate of technical success, b clinical success, c complete, and d partial clinical success.
significant difference in pooled rater of technical success (98.1% [95% CI, 94.3–99.4, I² = 0%] vs. 96.8% [95% CI, 88–99.2, I² = 0%], P = 0.55), clinical success (79.2% [95% CI, 53.3–92.7, I² = 89%] vs. 81.7% [95% CI, 49–95.4, I² = 54.9%], P = 0.87), complete clinical (63.4% [95% CI, 45.0–77.1, I² = 68.5%] vs. 71.6% [95% CI, 46.4–88, I² = 79.6%], P = 0.41) and partial clinical response (24.5% [95% CI, 14.9–37.7, I² = 0%] vs. 15.3% [95% CI, 6.6–31.7, I² = 45.4%], P = 0.3). The rates of AEs (16.5% [95% CI, 11.8–22.5, I² = 24.7%] vs. 20.7% [95% CI, 12.5–32.4, I² = 0%], P = 0.44), dysphagia (10.5% [95% CI, 7.1–15.3, I² = 0%] vs. 15.4% [95% CI, 8.4–26.5, I² = 0%], P = 0.28) and bleeding (4.4% [95% CI, 1.2–15.1, I² = 69.9%] vs. 5.9% [95% CI, 1.2–24.4, I² = 0%], P = 0.77) with ARMS were not significantly different than with ARMS-B. Results of subgroup analysis are summarized in Table 2.

### Table 2

| Study                  | Cases | Total | Proportion | 95% CI        |
|------------------------|-------|-------|------------|---------------|
| Bapaye et al. 2017     | 3     | 15    | 0.200      | [0.066; 0.470]|
| Debourdeau et al. 2020 | 2     | 6     | 0.333      | [0.084; 0.732]|
| Wong et al. 2020       | 5     | 33    | 0.152      | [0.065; 0.316]|
| Kessler et al. 2013    | 3     | 10    | 0.300      | [0.100; 0.624]|
| Prasad et al. 2019     | 0     | 11    | 0.000      | [0.003; 0.425]|
| Monino et al. 2020     | 4     | 21    | 0.190      | [0.073; 0.412]|
| Ortega et al. 2019     | 3     | 7     | 0.429      | [0.144; 0.770]|
| Patil et al. 2020      | 10    | 62    | 0.161      | [0.089; 0.275]|
| Sumi et al. 2020       | 17    | 109   | 0.156      | [0.099; 0.237]|
| Yoo et al. 2020        | 2     | 33    | 0.061      | [0.015; 0.212]|

**Random effects model**

- **Heterogeneity:** I² = 17%, τ² = 0.123, χ² = 9.17 (P < 0.42)

- **Study**
  - **Cases**
  - **Total**
  - **Proportion**
  - **95% CI**

- **Random effects model**

- **Heterogeneity:** I² = 0%, τ² = 0, χ² = 0 (P = 0.42)

- **Study**
  - **Cases**
  - **Total**
  - **Proportion**
  - **95% CI**

- **Random effects model**

- **Heterogeneity:** I² = 51%, τ² = 1.2360, χ² = 18.49 (P = 0.03)
Validation of meta-analysis results

Sensitivity analysis

To assess whether any one study had a dominant effect on the meta-analysis, we excluded one study at a time and analyzed its effect on the main summary estimate. On this analysis, no single study significantly affected the outcome or the heterogeneity.

Heterogeneity

We assessed dispersion of the calculated rates using the I^2 percentage values. I^2 provides information about what proportion of the dispersion was true vs a chance [29]. There was low heterogeneity in technical success and high heterogeneity in clinical success outcome. Calculated I^2 values are reported with pooled results.

Publication bias

Based on visual inspection of the funnel plot as well as quantitative measurement that used the Egger regression test, there was no evidence of publication bias for technical (Supplementary Fig. 2a, Eggers 2-tailed P = 0.07) and clinical success outcomes (Supplementary Fig. 2b, Eggers 2-tailed P = 0.09).
Discussion

Our study demonstrates that ARMS is a technically feasible and effective procedure for treatment of refractory GERD. It has a very high technical success rate of 97.7%. ARMS led to a significant discontinuation (65.3%) and reduction (21.5%) of PPI usage after the procedure. ARMS is also a relatively safe and well tolerated procedure. The rate of AEs is 17.2%, with dysphagia and bleeding being the most common complications. To our knowledge, this is the first systematic review and meta-analysis to assess the technical success, clinical response, and AEs of ARMS in refractory GERD.

We also report that ARMS significantly improves GERD-related symptoms. The GERD-HRQL scale is a disease-specific instrument, developed to help overcome variability in evaluating response to treatments for GERD and has been validated as a significant predictor of patient satisfaction. A reduction in the score by 50% or more is considered a successful intervention [30].

GERD-Q is a self-administered survey for GERD. It has a sensitivity of 65% and a specificity of 71% for diagnosis of GERD [31]. In our analysis, in post-ARMS, there was a significant decrease in GERD-HRQL (14.9) and GERD-Q (4.8) scores. While subjective scoring systems are biased by placebo effect of undergoing treatment, objective measures of AET and DeMeester scores do not have this limitation [32, 33]. In our analysis, post-ARMS, the mean AET decreased significantly by 2.39% and there was a trend toward improved DeMeester score but it did not reach statistical significance. Subgroup analysis was performed to compare ARMS with and without banding. It is important to note that both procedures were associated with similar technical success (98.1% vs 96.8%) without any significant difference. The addition of banding to EMR was not associated with a higher rate of AEs. The pooled rate of clinical success was not significantly different in patients undergoing ARMS (79.2%) when compared to ARMS-B (81.7%).

The most common AE was dysphagia from strictures. We reported a 11.4% risk of dysphagia in our analysis. Patil et al hypothesized that resection on more than two-thirds of the distal squamous esophageal mucosa is the cause of stricture formation [25]. Another hypothesis is that involvement of squamous mucosa in the resected area leads to a high occurrence of strictures [34]. Further, Sumi et al reported that patients undergoing crescentic resection had a higher risk of dysphagia when compared to those who had butterfly-shaped resection. Twelve of 81 patients had stenosis after crescentic resection while only one of 21 had stenosis after butterfly-shaped mucosal resection [26]. Although the strictures can be easily treated with endoscopic balloon dilation, there is a need to standardize the ARMS technique to prevent these AEs.

Approximately 40% of patients with GERD fail to respond to aggressive acid-suppressive therapy. Moreover, there are concerns about the long-term effects of PPI therapy as well. Because fewer than 5% of patients with refractory GERD undergo laparoscopic fundoplication, there is a treatment gap [3]. Newer, less invasive techniques have been developed to fill this gap, but with little success. The LINX reflux management system that augments the lower esophageal sphincter (LES) function using a small expandable ring of linked magnetic beads, Endostim LES stimulating system, and LES electrical stimulation therapy that use electrical energy to stimulate closure of LES are some of the alternative surgical approaches to refractory GERD treatment [8, 35, 36]. Several endoscopic models have also evolved to treat refractory GERD. Stretta utilizes a radiofrequency generator and a specialized balloon/catheter system that is used to remodel the EGJ and LES [37]. Medigus is an endoscopic stapling system that is capable of creating a partial fundoplication [38]. The newest approach is the TIF, which uses...
endoscopically placed polypropylene fasteners to create a 200–
to 270–degree fundoplication. Although there is initial im-
provement in symptoms, over time, the fasteners tend to dis-
lodge [39,40]. However, because of unclear long-term data, 
high economic burden, and inability to mitigate acid reflux, 
these procedures have not yet gained widespread acceptance.

Based on current literature, ARMS appears to be effective 
and well tolerated. The success of ARMS is likely related to its 
bility to cause submucosal fibrosis at LES. Relaxation of the 
cura and LES is a normal physiological process that occurs 
while swallowing. Transient lower esophageal relaxation 
(TLESR) is relaxation of the LES that is not initiated by swallow-
ing. TLESRs contribute to 90% of reflux episodes [41]. ARMS 
prevents the frequent occurrence of TLESRs. Recently, the 
ARMS technique has been further refined using a technique of 
anti-reflux mucosal ablation that causes similar scarring [42].

Proper patient selection was always performed for all the stud-
ies. Patients with hiatal hernia > 3 cm, esophageal motility dis-
orders, major psychiatric illness, and extremely obese were ex-
cluded. All patients underwent upper gastrointestinal endos-
copy, high-resolution manometry, and multichannel intra-
luminal impedance and pH monitoring prior to the procedure.

ARMS is usually performed using a cap-fitted EMR device. A 
variation of this technique, EMR with band ligation (ARMS-B) 
has been utilized in some studies. ARMS is performed by muco-
sal resection of more than two-thirds of the mucosa on the les-
ser curvature of the cardia below the gastroesophageal junc-
tion during retroflexed view in the stomach [34]. A small 
amount of mucosa is left in the lesser curvature in a butterfly 
shape to avoid transient stenosis. Rates of transient stenoses 
are significantly lower when a butterfly-shaped resection is 
performed when compared to the original crescent-shaped resec-
tion [26]. Care should be taken to avoid resection of squamous 
mucosa of the esophagus, which is associated with high rates of 
stricture formation. ESD is another method to achieve mucosal 
resection, but is associated with a higher rate of AEs [26]. After 
ARMS, a repeat endoscopic evaluation is performed in 2 to 3 
weeks to assess for stenosis. Patients are then assessed periodi-
cally after 2 months.

The strengths of this review are as follows: systematic litera-
ture search with well-defined inclusion criteria, careful exclu-
sion of redundant studies, inclusion of good quality studies 
with detailed extraction of data, low heterogeneity, studies 
from throughout the world, and rigorous evaluation of study 
quality. In addition, because we used both subjective and ob-
jective measures to quantify efficacy of clinical outcome, the 
results are generalizable. However, there are some limitations 
in this study, most of which are inherent to any meta-analysis. 
The included studies were not entirely representative of the general 
population and community practice, with most studies being 
performed in tertiary-care referral centers. The cost asso-
ciated with the procedure was not evaluated in our analysis. We 
were also unable to compare ARMS with the current standard of 
care for refractory GERD and laparoscopic fundoplication. Fur-
ther, the endoscopic procedure is highly operator-dependent. 
The success and safety profile are dependent on the expertise 
of the person performing the procedure. We also could not 
compare procedure time between the two techniques. In addi-
tion, follow-up was quite variable in included studies, which ad-
ded to heterogeneity for clinical success along with small sam-
ple size. There is limited precision in our estimates as evidenced 
by wide confidence intervals. We also could not directly com-
pare outcomes of ARMS with other endoscopic techniques 
such as TIF and MSA as data are not available. Additional sub-
group analyses were also not possible due to lack of data. 

Nevertheless, our study is the first meta-analysis evaluating the 
feasibility, effectiveness, and tolerability of ARMS.

Conclusions

In conclusion, ARMS seems to be an effective and well-tolerated 
endoscopic treatment strategy for refractory GERD. It is a less 
invasive technique that can fill the treatment gap between PPI 
therapy and laparoscopic fundoplication for treatment of re-
fractory GERD. Future prospective studies with long-term fol-
low up are needed to validate our findings.

Competing interests

The authors declare that they have no conflict of interest.

References

[1] Dent J, El-Serag HB, Wallander MA et al. Epidemiology of gastro-oe-
osphageal reflux disease: a systematic review. Gut 2005; 54: 710–717
[2] Miner PJr., Katz PO, Chen Y et al. Gastric acid control with esomepra-
ze, lanosoprazole, oneprazole, pantoprazole, and rabeprazole: a five-
way crossover study. Am J Gastroenterol 2003; 98: 2616–2620
[3] Subramanian CR, Triadafilopoulos G. Refractory gastroesophageal re-
flux disease. Gastroenterol Rep 2015; 3: 41–53
[4] Oelschlager BK, Quiroga E, Parra JD et al. Long-term outcomes after 
laparoscopic antireflux surgery. Am J Gastroenterol 2008; 103: 280– 
287 quiz 288
[5] Dominitz JA, Dire CA, Billingsley KG et al. Complications and antire-
flux medication use after antireflux surgery. Clin Gastroenterol Hep-
atol 2006; 4: 299–305
[6] Ganz RA, Peters JH, Horgan S. Esophageal sphincter device for gas-
 troesophageal reflux disease. N Engl J Med 2013; 368: 2039–2040
[7] Sanmiguel CP, Hagiike M, Mintchev MP et al. Effect of electrical stim-
ulation of the LES on LES pressure in a canine model. Am J Physiol 
Gastrointest Liver Physiol 2008; 295: C389–C394
[8] Bonavina L, Saino G, Bona D et al. One hundred consecutive patients 
treated with magnetic sphincter augmentation for gastroesophageal reflux 
disease: 6 years of clinical experience from a single center. J Am Coll 
Surg 2013; 217: 577–585
[9] Falk GW, Fennerty MB, Rothstein RI. AGA Institute technical review on 
the use of endoscopic therapy for gastroesophageal reflux disease. 
Gastroenterol 2006; 131: 1315–1336
[10] Inoue H, Ito H, Ikeda H et al. Anti-reflux mucosectomy for gastro-
esophageal reflux disease in the absence of hiatus hernia: a pilot 
study. Ann Gastroenterol 2014; 27: 346–351
[11] Moher D, Liberati A, Tetzlaff J et al. Preferred reporting items for sys-
tematic reviews and meta-analyses: The prisma statement. Ann Int Med 
2009; 151: 264–269
[12] Stroup DF, Berlin JA, Morton SC et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008–2012

[13] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Europ J Epidemiol 2010; 25: 603–605

[14] DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clin Trials 1986; 7: 177–188

[15] Sutton AJ, Abrams KR, Jones DR et al. Methods for meta-analysis in medical research. John Wiley & Sons Ltd New York 2000; 2000: 205–228

[16] Higgins JP, Thompson SG, Deeks JJ et al. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557

[17] Guyatt GH, Oxman AD, Kunz R et al. GRADE guidelines: 7. Rating the quality of evidence & inconsistency. J Clin Epidemiol 2014; 64: 1294–1302

[18] Easterbrook PJ, Gopalan R, Berlin JA et al. Publication bias in clinical research. Lancet 1991; 337: 867–872

[19] Bapaye A, Mahadik M, Pujari R et al. Antireflux mucosectomy (ARMS) for refractory GERD-Initial clinical experience. J Gastroenterol Hepatol 2017; 32: 255

[20] Debourdeau A, Vitton V, Monino L et al. Antireflux Mucosectomy Band (ARM-b) in treatment of refractory gastroesophageal reflux disease after bariatric surgery. Obesity Surg 2020; 30: 4654–4658

[21] Kessler WR, McNulty G, Lehman GA. A prospective, randomized study on the effect of band ligation with or without mucosectomy as a treatment for GERD: Pilot study, 12 month experience. Gastrointest Endosc 2013; 77: A8120

[22] Mohan Prasad VG, Appadarai S, Suman MP. Anti-reflux mucosectomy (ARMS) for refractory GERD-Our 3yrs experience. J Gastroenterol Hepatol 2019; 34: 232

[23] Monino L, Gonzalez JM, Vitton V et al. Antireflux mucosectomy band in treatment of refractory gastroesophageal reflux disease: a pilot study for safety, feasibility and symptom control. Endosc Int Open 2020; 8: E147–E154

[24] Ortega A, Roson P, Fernandez F et al. Antireflux mucosectomy, preliminary results of a prospective study. Endoscopy 2019; 51: S240–S241

[25] Patil G, Dalal A, Maydeo A. Feasibility and outcomes of anti-reflux mucosectomy for proton pump inhibitor dependent gastroesophageal reflux disease: First Indian study (with video). Digest Endosc 2020; 2020: 34: 745–752

[26] Sumi K, Inoue H, Kobayashi Y et al. Endoscopic treatment of proton pump inhibitor-refractory gastroesophageal reflux disease with antireflux mucosectomy: Experience of 109 cases. Dig Endosc 2021; 33: 347–354

[27] Wong HJ, Su B, Attaar M et al. Anti-reflux mucosectomy (ARMS) results in improved recovery and similar reflux quality of life outcomes compared to laparoscopic Nissen fundoplication. Surg Endosc Other Intervent Tech 2021; doi:10.1007/s00464-020-08144-9

[28] Yoo I, Ko WJ, Kim HS et al. Anti-reflux mucosectomy using a cap-assisted endoscopic mucosal resection method for refractory gastroesophageal disease: a prospective feasibility study. Surg Endosc 2020; 34: 1124–1131

[29] Mohan BP, Adler DG. Heterogeneity in systematic review and meta-analysis: how to read between the numbers. Gastrointest Endosc 2019; 89: 902–903

[30] Velanovich V, Vallance SR, Gusz JR et al. Quality of life scale for gastroesophageal reflux disease. J Am Coll Surg 1996; 183: 217–224

[31] Jones R, Junghard O, Dent J et al. Development of the GerdQ, a tool for the diagnosis and management of gastro-oesophageal reflux disease in primary care. Aliment Pharmacol Ther 2009; 30: 1030–1038

[32] Jamieson WR, Stein HJ, DeMeester TR et al. Ambulatory 24-h esophageal pH monitoring: normal values, optimal thresholds, specificity, sensitivity, and reproducibility. Am J Gastroenterol 1992; 87: 1102–1111

[33] Johnson LF, DeMeester TR. Development of the 24-hour intraesophageal pH monitoring composite scoring system. J Clin Gastroenterol 1986; 8: 52–58

[34] Shimamura Y, Inoue H. Anti-reflux mucosectomy: Can we do better? Dig Endosc 2020; 32: 736–738

[35] Lipham JC, DeMeester TR, Ganz RA et al. The LINX(R) reflux management system: confirmed safety and efficacy now at 4 years. Surg Endosc 2012; 26: 2944–2949

[36] Rodriguez L, Rodriguez P, Gomez B et al. Electrical stimulation therapy of the lower esophageal sphincter is successful in treating GERD: final results of open-label prospective trial. Surg Endosc 2013; 27: 1083–1092

[37] Triadafilopoulos G, Stretta: a valuable endoscopic treatment modality for gastroesophageal reflux disease. World J Gastroenterol 2014; 20: 7730–7738

[38] Danaloglu A, Cipe G, Toydemir T et al. Endoscopic stapling in comparison to laparoscopic fundoplication for the treatment of gastroesophageal reflux disease. Dig Endosc 2014; 26: 37–42

[39] Richter JE, Kumar A, Lipka S et al. Efficacy of laparoscopic Nissen fundoplication vs transoral incisionless fundoplication or proton pump inhibitors in patients with gastroesophageal reflux disease: a systematic review and network meta-analysis. Gastroenterology 2018; 154: 1298–1308 e1297

[40] McCarty TR, Itidiare M, Njei B et al. Efficacy of transoral incisionless fundoplication for refractory gastroesophageal reflux disease: a systematic review and meta-analysis. Endoscopy 2018; 50: 708–725

[41] Dodds WJ, Dent J, Hogan WJ et al. Mechanisms of gastroesophageal reflux in patients with reflux esophagitis. N Engl J Med 1982; 307: 1547–1552

[42] Tanabe M, Inoue H, Ueno A et al. Sa1255 A novel endoscopic fundoplication for gastroesophageal reflux disease; anti-reflux mucosal ablation (ARMA). Gastrointest Endosc 2019; 89: AB190