



# 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

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**BACKGROUND & AIMS:** The effects of transoral incisionless fundoplication (TIF) and laparoscopic Nissen fundoplication (LNF) have been compared with those of proton pump inhibitors (PPIs) or a sham procedure in patients with gastroesophageal reflux disease (GERD), but there has been no direct comparison of TIF vs LNF. We performed a systematic review and network meta-analysis of randomized controlled trials to compare the relative efficacies of TIF vs LNF in patients with GERD. **METHODS:** We searched publication databases and conference abstracts through May 10, 2017 for randomized controlled trials that compared the efficacy of TIF or LNF with that of a sham procedure or PPIs in patients with GERD. We performed a network meta-analysis using Bayesian methods under random-effects multiple treatment comparisons. We assessed ranking probability by surface under the cumulative ranking curve. **RESULTS:** Our search identified 7 trials comprising 1128 patients. Surface under the cumulative ranking curve ranking indicated TIF had highest probability of increasing patients' health-related quality of life (0.96), followed by LNF (0.66), a sham procedure (0.35), and PPIs (0.042). LNF had the highest probability of increasing percent time at pH < 4 (0.99), followed by PPIs (0.64), TIF (0.32), and the sham procedure (0.05). LNF also had the highest probability of increasing LES pressure (0.78), followed by TIF (0.72) and PPIs (0.01). Patients who underwent the sham procedure had the highest probability for persistent esophagitis (0.74), followed by those receiving TIF (0.69), LNF (0.38), and PPIs (0.19). Meta-regression showed a shorter follow-up time as a significant confounder for the outcome of health-related quality of life in studies of TIF. **CONCLUSIONS:** In a systematic review and network meta-analysis of trials of patients with GERD, we found LNF to have the greatest ability to improve physiologic parameters of GERD, including increased LES pressure and decreased percent time pH < 4. Although TIF produced the largest increase in health-related quality of life, this could be due to the shorter follow-up time of patients treated with TIF vs LNF or PPIs. TIF is a minimally invasive endoscopic procedure, yet based on evaluation of benefits vs risks, we do not recommend it as a long-term alternative to PPI or LNF treatment of GERD.

Gastroesophageal reflux disease (GERD) has an estimated prevalence of 18.1%–27.8% in North America.<sup>1</sup> GERD is currently the most common reason for outpatient gastrointestinal appointments, with an estimated 8.9 million outpatient visits, and the primary indication for upper endoscopy costing the health care system \$12.3 billion annually.<sup>2,3</sup> GERD is a chronic disease that impairs physical and psychological well-being resulting in decreased quality of life.<sup>4,5</sup> Initial treatment includes lifestyle modifications and medical therapy, with antireflux medications costing \$7.7 billion annually in the United States.<sup>6</sup> Despite following initial guideline recommendations of a 4- to 8-week trial of proton pump inhibitor (PPIs), 25%–42% of patients do not achieve symptomatic relief, and only 25% respond to twice-daily dosing.<sup>7</sup> Several observational studies report adverse associations with chronic PPI use (eg, dementia, osteoporosis, and pneumonia) raising fears of long-term use.<sup>8–12</sup>

Laparoscopic Nissen fundoplication (LNF) is a proven surgical therapy and is currently the gold standard for patients declining long-term PPIs.<sup>13</sup> The LNF employs minimally invasive techniques to completely dissect the esophageal hiatus and mobilize the gastroesophageal junction and esophagus; reduce the herniated gastroesophageal junction, cardia, and body back into the normal abdominal position; close the hiatal defect; divide the short gastric vessels to allow complete mobilization of the gastric fundus; and a 360° fundoplication not under tension.<sup>14</sup> This allows for re-creation of the 4 major components of a competent lower esophageal sphincter (LES). Cost–utility analysis comparing LNF to PPIs have

**Abbreviations used in this paper:** CrI, credibility interval; GERD, gastroesophageal reflux disease; HRQOL, health-related quality of life; LES, lower esophageal sphincter; LESP, lower esophageal sphincter pressure; LNF, laparoscopic Nissen fundoplication; NMA, network meta-analysis; OR, odds ratio; PPI, proton pump inhibitor; RCT, randomized controlled trial; SUCRA, Surface Under the Cumulative Ranking; TIF, transoral incisionless fundoplication.

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**Keywords:** HRQOL; Endoluminal; Esophagus; Hiatal Defect.

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**EDITOR'S NOTES****BACKGROUND AND CONTEXT**

The gold standard for anti-reflux surgery is the Nissen fundoplication. New endoscopic treatments such as transoral incisionless fundoplication (TIF) claim short term efficacy and safety but there are no direct comparisons.

**NEW FINDINGS**

LNF has the greatest durability to increase LES pressure and decreases % time pH<4 up to 5 years of follow-up. TIF was superior in symptom improvement over 6-12 months but not years. Perforation rate was high with TIF compared to LNF.

**LIMITATIONS**

There was no direct comparison between TIF and LNF necessitating network meta-analysis. Quality of studies varied from moderate to very low.

**IMPACT**

Until more good quality evidence is available including direct comparison to LNF, TIF cannot be recommended as an alternative to PPI or traditional Nissen fundoplication.

shown that LNF to be a more effective long-term strategy.<sup>15</sup> However, LNF is a technically exacting operation and not without adverse outcomes. Longer-term post-operative adverse events can occur in 15%–20% of patients, including gas-bloat syndrome, dysphagia, inability to belch, diarrhea, vagal nerve injury, and gastric dysmotility.<sup>16,17</sup>

To expand the number of GERD patients that can be treated with non-PPI strategies, several endoluminal therapies have been developed, including transoral incisionless fundoplication (TIF; EsophyX; EndoGastric Solutions, Redmond, WA),<sup>18</sup> Medigus Ultrasonic Surgical Endostapler (Medigus, Omer, Israel),<sup>19</sup> and Stretta (Mederi Therapeutics, Greenwich, CT).<sup>20</sup> Although the long-term efficacy has not been demonstrated with these endoscopic therapies, TIF has recently emerged as the most popular endoscopic therapy. However, TIF is not currently recommended as first-line therapy.<sup>13</sup>

TIF attempts to surgically restore competency to the LES, preventing reflux of gastric contents. Eligible candidates include intractable symptoms, no or mild esophagitis with hiatal hernia <2 cm, and abnormal acid reflux. The second of 2 improvements on this device, only the TIF 2.0 device (Esophyx, Endogastric Solutions) was included in our analysis. The basic features of the device and operation are detailed in [Figures 1A–1C](#). The valve created is between 200 and 270 degrees around the esophagus and between 3 and 5 cm in length ([Figure 1D](#)).<sup>21,22</sup>

Currently, the gold standard treatment for GERD remains long-term PPIs or LNF.<sup>13</sup> While both TIF and LNF have been compared with either PPIs<sup>22–27</sup> or sham,<sup>28,29</sup> TIF vs LNF has not been compared head to head. Accordingly, we performed a systematic review and network meta-analysis of randomized controlled trials (RCTs) to assess the efficacy of TIF vs LNF for GERD.

**Methods**

This systematic review was performed following the standard methodology prespecified in a protocol available at [10.6084/m9.figshare.5043205](https://doi.org/10.6084/m9.figshare.5043205).<sup>30</sup>

**Search Methods**

An electronic search of MEDLINE, Cochrane Central Register of Controlled Trials, and EMBASE using a combination of MeSH and free text from inception to inception to May 10, 2017 was performed. The detailed search strategy is illustrated in the [Supplementary Material](#).

To identify any recently completed studies that have not yet been published in full, we searched conference abstracts from the last 3 meetings (2014–2016) of the American College of Gastroenterology and Digestive Disease Week. We also hand searched references of all identified review articles and included studies.

**Selection Criteria**

RCTs evaluating the efficacy of TIF or LNF with sham or medical treatment for the management of GERD were eligible for inclusion. In eligible RCTs, GERD was established by the presence of erosive esophagitis on endoscopy and/or abnormal ambulatory esophageal pH monitoring (defined by Demeester score >14.7 and/or percentage total time pH <4 of  $\geq 4.0\%$ ) and quality of life surveys or by symptom scores who were previously on PPIs. As would be expected, the TIF studies had milder esophagitis and small hiatal hernias (<2 cm), while the LNF studies included all grades of esophagitis (LA grade A–D) and sizes of hiatal hernia. Studies that were nonrandomized or included specialized treatment groups (eg, post-reflux surgery/obese patients) were excluded.

Three authors independently reviewed all titles/abstracts and selected full-text articles for inclusion. We searched references of eligible studies to identify additional studies. Two authors (SL, JR) independently extracted data on outcomes from all studies using a standardized abstraction form.

**Data Collection and Analysis**

Four authors (SL, AK, VV, and JR) reviewed all titles, abstracts, and full-text reports independently. Any disagreements between authors during the study selection were resolved by consensus.

**Data Extraction and Management**

Broadly, we extracted data on author names, location and setting, specific intervention and comparison details, outcomes and participants.

Three authors (SL, AK, and JR) independently extracted data using a standardized data extraction form containing the following items:

- General information: study title, authors, sources
- Study characteristics: study design, setting, duration of follow-up
- Patient characteristics: number of patients enrolled, number of patients included in the analysis

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