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Australia and New Zealand Horizon Scanning Network

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TERRITORY GOVERNMENTS OF AUSTRALIA  
AND THE GOVERNMENT OF NEW ZEALAND

# **Horizon Scanning Technology Prioritising Summary**

## **EsophyX™ System**

**February 2009  
(Updated April 2010)**



**Australian  
Safety  
and Efficacy  
Register  
of New  
Interventional  
Procedures -  
Surgical**



**Royal Australasian  
College of Surgeons**

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## **IMPACT SUMMARY**

The EsophyX™ Transoral Incisionless Fundoplication system (EndoGastric Solutions, Washington, United States) treats gastro-oesophageal reflux disease (GORD) by reconstructing the gastro-oesophageal valve, accessing it via the oesophagus. The technology is appropriate for GORD patients that are responsive to pharmacological therapy, and is available through gastroenterologists.

## **BACKGROUND**

Gastro-oesophageal reflux disease (GORD) is a mechanical disorder in which a defective lower oesophageal sphincter does not close and stomach contents reflux into the oesophagus (Smith 2008).

The most common symptoms experienced by GORD sufferers include heartburn, regurgitation, dysphagia and chest pain (Kahrilas 2008). Other, less common symptoms include odynophagia, excessive salivation and nausea (Kahrilas 2008).

GORD can result in injury to the oesophagus leading to conditions such as reflux oesophagitis, oesophageal strictures, Barrett's oesophagus and oesophageal adenocarcinoma (Kahrilas 2008).

Treatment for GORD generally follows one of two main pathways, pharmacological or surgical. Pharmacological therapy involves the long term use of anti-reflux medications to control GORD symptoms, while surgical therapy generally involves a procedure to strengthen the gastro-oesophageal valve. Regardless of the pathway selected, treatment of GORD almost always includes lifestyle modifications such as (Kaltenbach et al 2006; Piesman et al 2007):

- Weight loss
- Elevating the head of the bed
- Avoiding eating two hours before bedtime
- Dietary changes

While the use of proton pump inhibitors (PPI) in pharmacological therapy as the first treatment option often results in significant symptom control, PPIs do not address the mechanical causes of the condition (Cadiere et al 2008a; Malik et al 2006). Furthermore, the inconvenience of long-term, daily medication may result in patient dissatisfaction and non-compliance (McLoughlin et al 2006).

The Nissen fundoplication procedure is the current gold standard treatment for GORD, with 89.5% of patients remaining symptom-free at 10 years (Bergman et al 2008). The procedure is often performed laparoscopically and involves wrapping the stomach around the lower oesophageal sphincter to strengthen the closing function of the sphincter (preventing acid reflux) and to repair hiatal hernias. The procedure however, is associated with serious potential complications including dysphagia, bloating, nausea, vomiting and other symptoms related to vagal nerve injury (Waring et al 1999). Furthermore, while re-

operation is possible, extensive scarring from the initial procedure makes re-operation more technically challenging.

Endoluminal fundoplication using the EsophyX device is a novel minimally invasive procedure. The procedure involves the insertion of the EsophyX device transorally, under direct endoscope visualisation, into the stomach to facilitate the reconstruction of the gastro-oesophageal valve (Cadiere et al 2006). The result is a 3 cm to 5 cm long omega-shaped valve with a 200° to 310° circumference. The device facilitates the creation of the valve by drawing gastric tissue from the fundus between the body of the device and the tissue mould used to shape each portion of the gastro-oesophageal valve. Multiple polypropylene fasteners are then delivered across the moulded tissue to create a serosa to serosa flap 3 cm to 5 cm long. The repair of hiatal hernias is achieved through a proprietary oesophageal invaginator incorporated into the device, which engages the distal oesophagus at the level of the Z line.

#### **CLINICAL NEED AND BURDEN OF DISEASE**

GORD is a common condition and accounts for approximately 75% of all oesophageal pathologic findings (Smith 2008). In Western countries it is estimated that the condition affects between 10% and 20% of the population (Dent et al 2005). Furthermore, approximately half of all GORD sufferers experience symptoms for more than 10 years (Dent et al 2005). No data regarding the incidence or prevalence of GORD in Australia was identified in the searches conducted.

Approximately 44% of Americans experience monthly heartburn with 18% of these requiring non prescription medications. GORD has a prevalence of approximately 19 million cases per year in the United States with a total cost of care of US\$9.8 billion (Richter 2007).

An endoluminal, minimally invasive approach to anti-reflux surgery, such as that presented by the EsophyX fundoplication procedure, has many potential advantages. These advantages may include leaving the gastro-oesophageal junction intact, the ability to perform the operation as an outpatient procedure, reduced operating time, a potential reduction in hospital costs and potential for future medical or surgical therapy.

#### **DIFFUSION**

The literature published for the use of the EsophyX system originates primarily from Europe. The EsophyX system received clearance from the United States Food and Drug Administration (FDA) in 2007 and has also received the European CE mark.

There is currently no literature documenting the use of the EsophyX system in Australia, and the device is not listed on the Australian Register of Therapeutic Goods (ARTG).

#### **COMPARATORS**

The gold standard surgical treatment for GORD is the Nissen fundoplication procedure. However, minimally invasive endoscopic techniques have been developed to address

some of the complications and difficulties associated with surgery. These techniques can be divided into three categories: thermal ablation techniques, endoluminal gastric plication, and injection/implantation techniques:

Other endoscopic treatments for GORD include (McLoughlin et al 2006):

- Thermal ablation techniques: Stretta® Procedure<sup>1</sup> (Curon® Medical, Inc., California, United States),
- Endoluminal gastric plication: Bard® EndoCinch™<sup>1</sup> (C.R. Bard, Inc., New Jersey, United States), Wilson-Cook Endoscopic Suturing Device (Wilson-Cook Medical, Inc., North Carolina, United States), NDO Plicator™<sup>1</sup> (NDO Surgical, Inc., Massachusetts, United States),
- Injection/implantation techniques: Enteryx®<sup>1</sup> (Boston Scientific Corporation, Massachusetts, United States), Gatekeeper™ Reflux Repair System<sup>1</sup> (Medtronic, Inc., Minnesota, United States) and Plexiglas®.

### **SAFETY AND EFFECTIVENESS ISSUES**

Bergman et al (2008) reported on a retrospective study of eight (four male and four female) consecutive GORD patients (mean age  $49 \pm 21$  years) who underwent endoluminal fundoplication using the second generation EsophyX device. Each patient had an American Society of Anaesthesia Index (ASA)  $\leq 3$ , and a body mass index (BMI)  $\leq 40$  kg/m<sup>2</sup>, did not have had a hiatal hernia  $> 2$  cm, and did not present with any severe gastro-oesophageal pathology or motility disorder. Seven patients were using PPI therapy prior to the procedure (one patient, intolerant to PPIs was taking antacids 10-15 times a day), four patients had small ( $\leq 2$  cm) hiatal hernias and four had oesophagoduodenoscopy evidence of GORD.

Cadiere et al (2008a) reported the results of a prospective study involving nineteen consecutive patients who underwent endoluminal fundoplication using the EsophyX device. The patients presented with chronic (median duration 10 years; range: 3 to 15 years), symptomatic GORD, requiring daily PPI therapy (median time on PPI therapy 6 years; range: 2 to 13 years) with no evidence of oesophageal motility disorder. The presence of an oesophageal stricture in one patient and a 6 cm hiatal hernia in another led to the exclusion of two patients. Baseline assessment of GORD-HRQL and pH required patients to discontinue PPI therapy for at least seven days before measurements could be taken. However, due to the return of symptoms, baseline measurements were performed under PPI therapy. Following the procedure, patients were instructed to stop PPI therapy for seven days and contact the study coordinator in case of any complications or adverse events. In total, 17 patients (seven males and 10 females) with a median age of 34 years (range: 23 to 58 years) and a median BMI of 22 kg/m<sup>2</sup> (range: 18 to 31 kg/m<sup>2</sup>) were included.

Cadiere et al (2008b) reported the results of a prospective multicentre study involving 86 patients (29 female and 57 male, median age 44 years) suffering chronic GORD (median duration 6 years) undergoing daily PPI therapy (median duration four years). Patients

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<sup>1</sup> No longer on the market.

were responsive to PPI therapy, as indicated by GORD-HRQL scores of  $\leq 12$ ; however they experienced symptom recurrence upon discontinuation of PPI therapy for 14 days (GORD-HRQL score  $\geq 20$  or difference of  $\geq 10$  between the scores on and off PPIs). PPIs were discontinued for 14 days, and other GORD medications were discontinued for at least two days, prior to administration of the GORD-HRQL questionnaire. Seven days after surgery, patients were instructed to discontinue PPIs.

### **Safety**

The mean procedural time reported by Bergman et al (2008) was  $85 \pm 30$  minutes. During the peri-operative period, no complications were reported. During the postoperative follow-up period, at  $60 \pm 44$  days following the procedure, Bergman et al (2008), recorded no postoperative adverse events. However, at seven days postoperatively, one patient experienced a sudden onset recurrence of heartburn. An oesophagoduodenoscopy revealed that the patient had lost more than half of the fasteners and had a gastro-oesophageal valve resembling his pre-procedural state. The aetiology of this finding was reported as unknown.

The median procedural time reported by Cadiere et al (2008a) was 123 minutes (range: 55 to 254 minutes). The authors reported no serious complications such as perforation, bleeding or death during the immediate perioperative period. On the first day following the procedure, 11 patients (65%) reported pharyngeal irritation resulting from device insertion and manipulation, however none complained of dysphagia. Mild epigastric pain was reported by all patients and treated with analgesics. One patient reported transient dysphonia. There was one readmission during the first postoperative week. This patient had air in the upper abdomen and had no evidence of perforation. The patient required no intervention and was discharged without further sequelae. Other adverse events including bloating, diarrhoea, difficulty swallowing, eructation, fever, flatulence, haematemesis, left shoulder pain, and nausea and vomiting were reported from the first postoperative day, however, their incidence decreased substantially during the first two postoperative weeks.

Cadiere et al (2008b) reported a median procedural time of 77 minutes (range: 28 to 208 minutes). A variety of non-serious adverse events, which resolved spontaneously, were reported by the authors. Musculoskeletal pain in the left shoulder for up to one month was the most common of these adverse events ( $n = 8$ ). Musculoskeletal left shoulder pain was most likely a result of the requirement for patients to be positioned on their left side to conduct the procedure. Other adverse events which lasted for up to one month included upper abdominal pain in four (5%) patients, pharyngolaryngeal pain in one (1%) patient and epigastric pain in two (2%) patients. One case of upper abdominal pain (1%) and one case of nausea (1%) were reported to last over one month. Three serious adverse events were reported, including one case of perforation of the proximal oesophagus during advancement of the device without adequate visualisation, one case of perforation during an attempted device insertion into the narrow hypopharynx of a patient with Turner's syndrome and one case of post-procedural intraluminal bleeding with accompanying decrease of haemoglobin of  $70 \text{ g L}^{-1}$ . In both perforation cases, the injury was able to be successfully repaired surgically. In the patient with intraluminal bleeding, the bleeding

was able to be controlled by the use of clips and fibrin glue, as well as a blood transfusion.

### **Effectiveness**

Bergman et al (2008) achieved a mean valve geometry of  $238^{\circ} \pm 31^{\circ}$  with a mean valve length of  $3.2 \pm 0.6$  cm. Patients were instructed to stop PPI therapy seven days after the procedure unless symptoms persisted. The GORD health-related quality of life (GORD-HRQL) and symptom severity scale were then administered during the follow-up period between four and six weeks post-operatively (mean follow-up  $60 \pm 44$  days). The mean post-operative GORD-HRQL score was  $8 \pm 8$ , while the postoperative mean severity score was  $17 \pm 15$ . The baseline values for these parameters however, were not reported. At the time of follow-up, four patients (including the patient with lost fasteners) were on the same PPI dose as before the procedure. Additionally, these patients reported being either neutral or dissatisfied with their post-operative condition. Two patients no longer required PPI therapy and a further two were taking  $\leq 50\%$  of their pre-operative PPI or antacid doses. These patients reported lower GORD-HRQL ( $3.3 \pm 2.6$  versus  $12.5 \pm 8.4$ ;  $p = 0.08$ ) and symptom severity scores ( $4.8 \pm 4.8$  versus  $28.8 \pm 11.2$ ;  $p = 0.01$ ), and were satisfied with their post-operative condition.

The patients reported by Cadiere et al (2008a) achieved a median immediate postoperative valve geometry and length of  $210^{\circ}$  (range:  $180^{\circ}$  to  $270^{\circ}$ ) and 4 cm (range: 3 cm to 5 cm), respectively. At 12 months postoperatively, the median valve geometry and length was  $200^{\circ}$  (range:  $150^{\circ}$  to  $210^{\circ}$ ) and 3 cm (range: 1 cm to 4 cm), respectively. During the baseline period, upper gastrointestinal endoscopy demonstrated evidence of reflux oesophagitis in all patients (13 patients grade A, two patients grade B and two patients grade C, according to the Los Angeles classification<sup>2</sup>). Postoperatively at 12 months, grade A or grade B oesophagitis was observed in 13 patients with no evidence of grade C oesophagitis in any patient. Similarly, during the baseline period, the natural gastro-oesophageal valves of all patients appeared loose around the endoscope. Immediately following the procedure, 14 valves were assessed as being tight around the endoscope, while three were assessed as moderate around the endoscope. At 12 months post-operatively, qualitative upper gastrointestinal endoscopic evaluation performed in 16 patients demonstrated that adherence of the gastro-oesophageal valve to the endoscope was tight in one patient, moderate in 12 patients and loose in three patients.

The primary end-point of the study was improvements of  $\geq 50\%$  at 12 months in GORD-HRQL. Patients who met this criterion were considered to be responsive to the procedure. The median baseline GORD-HRQL was 17 (range: 12 to 31). At 12 months, all patients on PPIs discontinued medication for 15 days prior to the GORD-HRQL assessment. A significant ( $p = 0.02$ ) 67% improvement in post-operative GORD-HRQL to a median of

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<sup>2</sup> Los Angeles Classification of Oesophagitis:  
Grade A - Mucosal break  $\leq 5$  mm in length  
Grade B - Mucosal break  $> 5$  mm in length  
Grade C - Mucosal break continuous between  $> 2$  mucosal folds  
Grade D - Mucosal break  $\geq 75\%$  of oesophageal circumference

six was reported in the 17 patients. Nine patients (53%) recorded a GORD-HRQL score improvement of  $\geq 50\%$ .

Secondary end-points included improvement in the percentage of time at  $\text{pH} < 4$  and a reduction in the use of PPIs. Fourteen patients (82%) were able to discontinue daily PPI therapy and 10 (63%) of the 16 patients who completed the 48 hour pH assessment demonstrated normal oesophageal acid exposure at 12 months post-operatively.

Success was defined as acid exposure equal to or less than 5.3% of time at  $\text{pH} < 4$  (normal pH) and elimination of PPI therapy. Ten out of 16 patients and 14 out of 17 patients achieved normal pH and stopped PPI usage, respectively.

Preoperatively, thirteen (76%) patients had a reducible hiatal hernia (median size 2 cm; range: 1 cm to 3 cm). Following the procedure, all hiatal hernias had been completely reduced. At 12 months postoperatively, hiatal hernias remained reduced in 62% (8/13) of patients.

Follow-up at 12 months showed that 82% of patients were satisfied or very satisfied with the procedure.

Cadiere et al (2008b) reported a median valve length of 4 cm (2 cm to 6 cm) and geometry of  $230^\circ$  ( $160^\circ$  to  $300^\circ$ ). The authors reported that 81 (96%) patients at six months and 79 (94%) patients at 12 months were available for effectiveness analyses.

Prior to the procedure, the authors reported an increase in the median GORD-HRQL and heartburn scores upon discontinuation of daily PPIs from 9 (range: 0 to 22) to 24 (range: 11 to 38) and from 7 (range: 0 to 19) to 21 (range: 10 to 30) respectively. At six months postoperatively, patients reported a median reduction in GORD-HRQL of 80%, with a median GORD-HRQL score of 5 (range: 0 to 24), a statistically significant difference to the baseline score ( $p < 0.0001$ ). At this time, 62 (77%) patients had recorded a clinically significant GORD-HRQL improvement of  $\geq 50\%$ . At 12 months, the median GORD-HRQL reduction was 68% (median GORD-HRQL: 7; range: 0 to 30), which was statistically significant when compared to the baseline score ( $p < 0.0001$ ). At 12 months, the number of patients with a clinically significant reduction in GORD-HRQL score was 58 (73%).

The number of patients in whom complete postoperative GORD symptom elimination had occurred (GORD-HRQL score  $\leq 12$ ) was 65 (80%) at six months, and 59 (75%) patients at 12 months. The median post-operative reduction in GORD-HRQL in comparison to the baseline scores (while on PPIs) was 50% ( $p < 0.05$ ) at six months, but decreased to 22% ( $p = \text{NS}$ ) at 12 months.

The changes in heartburn score following the procedure were similar to those observed for the GORD-HRQL. The median heartburn score at 12 months was 6 (range: 0 to 26), a 67% reduction on baseline scores ( $p < 0.0001$ ). When compared to the on PPIs baseline

scores however, the median percentage reduction was significant at six months ( $p < 0.05$ ), but not at 12 months.

At baseline, 8% of patients were taking a double dose of PPIs, 43% a full dose and 49% a half dose. At six months postoperatively, this reduced to 4% on double dose, 6% on full dose, 7% on half dose, and 14% on demand, while 69% ( $n=81$ ) of patients were not taking any PPIs. At 12 months, 10% of patients were on full dose, 5% on half dose and 18% on demand, while 67% were no longer taking PPIs. Prior to the procedure, all patients were taking some sort of GORD medication daily. Postoperatively, at six months 14 (17%) patients required daily medication, 25 (31%) required occasional medication and 42 (52%) no longer required any GORD medication. At 12 months, 12 (15%) patients required daily medication, 29 (37%) required occasional medication and 38 (48%) no longer required medication.

At baseline, 58% of patients had a hiatal hernia with a median size of 1 cm (range: 1 cm to 3 cm). Following the procedure, all hiatal hernias were successfully reduced.

Prior to the procedure, the gastro-oesophageal valves were mostly Hill grade<sup>3</sup> II (approximately 45%) or grade III (approximately 40%). At six months, this had improved to approximately 30% grade I, 55% grade II, 10% grade III and 5% grade IV. At 12 months, approximately 32% were grade I, 35% grade II, 25% grade III and 7% grade IV.

The mean baseline lower oesophageal sphincter resting pressure in 77 patients was 13.1 mmHg (range: 4 to 30 mmHg). Postoperatively in 75 patients, this significantly improved ( $p < 0.01$ ) by 53% to 18.2 mmHg (range: 4 to 43).

Oesophageal acid exposure time was significantly reduced or normalised in 43 (61%) patients at 12 months postoperatively. This was equivalent to a median percentage reduction in time  $\text{pH} < 4$  of 33% at 12 months ( $p = 0.02$ ).

Based on the clinically significant reduction of heartburn, complete cessation of PPIs, and normalisation/significant reduction of oesophageal acid exposure in 80% of cases, 45 (56%) patients were considered to be cured. Of these cured patients, 19 (24%) patients were considered completely cured, defined by elimination of symptoms, oesophagitis and hiatal hernia as well as normalisation of oesophageal acid exposure. Twenty-two percent of patients were considered as improved, defined by 80% reduction in symptoms, cessation of daily PPIs, and reduced hiatal hernia or oesophagitis. The remaining 22% of patients were considered to have ongoing GORD, defined by the continuation of GORD symptoms and daily requirement for PPI therapy.

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<sup>3</sup> Hill grades:

Grade I valves – presence of prominent tissue fold surrounding the endoscope

Grade II valves – presence of moderately prominent tissue fold which rarely opens with respiration and closes promptly

Grade III valves – barely present fold which fails to close around the endoscope

Grade IV valves – absence of muscular fold. The lumen of the oesophagus remains open all the time allowing squamous epithelium to be viewed from the top.

### **COST IMPACT**

No cost information relating to the EsophyX system was identified from the retrieved studies.

### **ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS**

No other issues were identified from the retrieved studies.

### **OTHER ISSUES**

No other issues were identified from the retrieved studies.

### **SUMMARY OF FINDINGS**

Endoluminal fundoplication using the EsophyX system results in gastro-oesophageal valves similar to that achieved with Nissen fundoplication. Evidence from the identified studies suggests that the device and the procedure are safe. However, while results in terms of the GORD-HRQL and other effectiveness measures appear favourable, there is a need for randomised controlled trials comparing endoluminal fundoplication using the EsophyX system to current standard medical and surgical treatment options.

### **HEALTHPACT ACTION**

Based on the limited evidence available and the potential of the technology to provide a minimally invasive alternative to Nissen fundoplication, this technique is monitored for 12 months.

### **NUMBER OF STUDIES INCLUDED**

Total number of studies        3  
Level IV intervention evidence

### **REFERENCES**

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**SEARCH CRITERIA TO BE USED**

Fundoplication

Nissen fundoplication

GORD

GERD

Gastroesophageal reflux disease

Gastro-oesophageal reflux disease

Endoluminal

Minimally invasive

EsophyX

Transoral incisionless fundoplication

TIF

# PRIORITISING SUMMARY (UPDATE 2010)

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<b>NAME OF TECHNOLOGY</b>	<b>ESOPHYX™ SYSTEM</b>
<b>PURPOSE AND TARGET GROUP</b>	<b>FOR THE TREATMENT OF SYMPTOMATIC CHRONIC GASTRO-OESOPHAGEAL REFLUX DISEASE IN PATIENTS RESPONSIVE TO PHARMACOLOGICAL THERAPY</b>

## **2010 SAFETY AND EFFECTIVENESS ISSUES**

### *Study descriptions*

A search of the literature identified four case series studies reporting the use of the EsophyX system. Three studies, with the largest patient population and longest follow-up, were selected for inclusion in this update (Repici et al 2010; Demyttenaere et al 2009; Cadiere et al 2009). The case series study by Cadiere et al (2009) was a follow-up study reporting 2-year outcomes in patients previously reported in two studies included in the original summary (Cadiere et al 2008a; Cadiere et al 2008b).

The prospective, single-arm study by Repici et al (2010) aimed to test the hypotheses that endoscopic fundoplication would decrease the use of antisecretory drugs, decrease GORD symptoms, improve quality of life, and reduce oesophageal acid exposure. Between June 2006 and April 2008, 64 consecutive patients presenting with a history of chronic reflux oesophagitis (>6 months) and requiring long-term acid suppressive therapy were considered for inclusion. An initial screening phase involving evaluation of their medical history (including GORD medication usage) and completion of a GORD health-related quality of life (HRQL) questionnaire (while they remained on PPI therapy). The same HRQL questionnaire was re-administered once PPI usage was discontinued for  $\geq 21$  days, along with 24 hour pH-impedance monitoring. Normal manometry and pH-impedance values were defined as: basal LES pressure from 8-26.5mmHg, residual LES pressure <4mmHg, acid percent time <1.1%, and all reflux percent time <1.4%.

Of the 64 potential patients only 20 (15 men, 5 women; median age 47.5 years, range: 26-68 years) met stringent inclusion criteria, including: having symptomatic gastro-oesophageal reflux defined by GORD-HRQL score >20 (whilst off acid suppression therapy), and deterioration of gastro-oesophageal junction with Hill grade II, III, or IV. Patients were also excluded if they had hiatal hernia larger than 3cm, oesophageal motility disorders, diverticula, strictures, previous gastro-oesophageal surgery, or Barrett's oesophagus. At baseline, 55% of patients with small hiatal hernia (<3cm), 25% with grade B/C oesophagitis (according to the Los Angeles classification), and 8, 10, and 2 patients had Hill grade II, III and IV, respectively. Pretreatment mean pressure of the lower oesophageal sphincter was  $10.5 \pm 2.7$  mmHg (range, 6-15), and mean total reflux time and acid reflux time was 3.8% and 2.8%, respectively.

Following the procedure patients were instructed to discontinue PPI medication for 5 days. If symptoms returned PPI treatment (maintenance or on demand) was restarted, and patients were free to adjust their daily dose as desired/depending on symptoms (use of other antacids was discouraged). At one-month postoperative, patients underwent a clinic or telephone interview where the GORD-HRQL and symptom severity scale were administered and PPI consumption, present symptoms, and the occurrence of adverse events were recorded. Stationary manometry and ambulated 24 hour pH-impedance monitoring, as well as endoscopy, were performed again at 6- and 12-months follow-up. Six month follow-up was completed by 100% (20/20) of patients and 12-month follow-up by 75% (15/20).

In the study by Demyttenaere et al (2009) prospective data was collected on consecutive patients undergoing EsophyX fundoplication between September 2007 and March 2009. The aim of the study was to investigate the safety and efficacy of the EsophyX procedure. The inclusion criteria for patients opting to undergo the procedure included being aged 18-80 years, having documented GORD, taking PPIs for  $\geq 6$  months, and normal or reduced manometry. Exclusion criteria included BMI greater than  $40\text{kg/m}^2$ , grade D oesophagitis, pregnancy, or moderate to large hiatal hernias ( $>3\text{cm}$ ). A total of 26 patients were eligible for inclusion. Three patients were lost to follow-up and another withdrew from the study (with a complication); therefore, complete follow-up data was available for a total of 22 patients (mean age 45 years  $\pm$  15 years standard deviation). Preoperatively, 50% (11/22) of patients had small hiatal hernia, 14% (3/22) had biopsy-proven Barrett's oesophagus, 23% (5/22) had oesophageal dysmotility, and 5% (1/22) had oesophageal stricture.

All patients underwent a routine antireflux surgery workup including endoscopy, pH studies, and video oesophagram. Oesophageal manometry was only performed when symptoms or an abnormal video barium oesophagram indicated it was necessary. A self-reported symptom severity score was obtained, along with a GORD-HRQL score prior to surgery. Following the procedure, patients were seen for a clinic assessment at 2-4 weeks. At this time a history, physical examination, and review of symptoms and medications were performed. Follow-up phone calls were made every 3 months thereafter to evaluate medication use and patient satisfaction. Mean follow-up period was 10 months.

Cadiere et al (2009) conducted a single-centre feasibility study where patients with chronic symptomatic GORD lasting more than 6 months, a small hiatal hernia, receiving daily PPI therapy, and showing anatomic deterioration of their oesophagogastric junction were enrolled. Patients were excluded if they had a BMI  $\geq 30\text{kg/m}^2$ , oesophagitis grade D (using the Los Angeles classification), irreducible hiatal hernia  $>3\text{cm}$ , oesophageal or gastric emptying diseases, or previously failed antireflux procedures. Initial screening assessment was conducted while patients were still using PPIs and included the GORD-HRQL questionnaire, 24 hour ambulatory pH-metry, upper GI endoscopy, oesophageal biopsy, oesophageal manometry, medical history, and GORD medication usage. Each patient's ability to consume food/beverages commonly linked with GORD symptoms was also assessed by asking patients if they were able/unable to consume each food without symptoms. The effect of GORD on lifestyle was also measured by asking patients

whether they could eat late at night, smoke, drink alcohol, or exercise 1 hour after a meal without GORD symptoms. Follow-up assessment at 2 years consisted of the same tests used in the preoperative screening assessment and results were compared. Global assessments of all outcome measures were performed for each patient to determine the long-term effectiveness of transoral incisionless fundoplication in curing GORD. Patients were considered cured if: they no longer had heartburn/regurgitation, oesophagitis and hiatal hernia were eliminated, and PPI use was discontinued. Patients were considered improved if: they had reduced heartburn, oesophagitis, or hiatal hernia, and only required occasional PPIs.

A total of 14 patients (82%) were available for follow-up at 2-years (50% women, median age 34 years, range: 23-55 years). Two patients underwent retreatment (with laparoscopic Nissen and TIF2, respectively) because they continued to experience GORD symptoms and a third patient was lost to follow-up due to lack of contact. The retreated patients were considered failures per intent-to-treat analysis and were omitted from analysis of efficacy data per protocol. The median time patients suffered from GORD before undergoing the procedure was 10 years (range, 3-15) and PPI usage spanned a median of 6 years (range, 2-13 years). At baseline, median GORD-HRQL score whilst on PPIs was 17 (range, 12-31), upper endoscopy showed evidence of loose adherence of the oesophagogastric junction and reflux oesophagitis in all patients, and sliding hiatal hernia with 2cm or 3cm lengths was apparent in 7 and 3 patients, respectively. Overall, mean follow-up was 25 months (range, 24-27 months).

### *Safety*

No major intraoperative complications were encountered in the study by Repici et al (2010). Two serious adverse events were reported on the first and eighth postoperative days respectively. They were haematemesis in two patients, requiring either prolonged hospitalisation or rehospitalisation. Both patients were treated conservatively.

Procedural complications occurred in two patients in the study by Demyttenaere et al (2009). One patient was an 18 year old woman with cystic fibrosis who had undergone remote Nissen fundoplication at 6 months of age and the other was a 43 year old woman. Both women were tachycardic at the time of their procedure, and both were transfused and underwent upper endoscopy. Their hospital stays were 3 and 6 days respectively. In addition, many patients reported sore throats and left shoulder pain on the first postoperative day. These issues were self-limiting and resolved within the first postoperative week. Other patient complaints included sharp chest pain (n=2) and nausea and vomiting (n=1). The patients with chest pain experienced it during the first postoperative week and were subsequently given a cardiac workup revealing no abnormalities. The remaining patient experiencing nausea and vomiting was readmitted into hospital on day 3 where diagnostic tests were undertaken; all results were normal and the patient was rehydrated and discharged.

In the study by Cadriere et al (2009) no adverse events related to the EsophyX procedure occurred between the 1- and 2-year follow-up visits.

### *Effectiveness*

In the study by Repici et al (2010) the mean duration of the procedure was 62 minutes (range, 38-105 minutes). At 6 months follow-up 55% (11/20) of patients were off PPIs and free from GORD symptoms and nine patients resumed PPI or H2 blockers. Endoscopy showed grade B oesophagitis in 5% (1/20) of patients. Most patients were Hill grade I (n=12) or II (n=6) following their procedure and 2 patients were grade III. At the same time GORD-HRQL score dropped from a median of 40 to a median of 7 from preoperative to postoperative testing ( $P<0.05$ ). Both stationary manometry and pH-impedance outcomes were not significantly different at 6 months follow-up. Four patients with persistent GORD symptoms despite PPI usage opted to undergo laparoscopic fundoplication and were excluded from further follow-up. Another patient was lost to follow-up after 6 months. Of the 15 patients who completed 1-year follow-up 47% (7/15 patients) remained off PPIs and 73.3% (11/15 patients) had a greater than 50% improvement in GORD-HRQL score. Again, stationary manometry did not show significant changes from preoperative measurements, as did total (3.3%) and acid (2.7%) reflux oesophageal exposures. Another two patients opted for laparoscopic surgery at this time due to persistent symptoms as a result of pathologic acid oesophageal exposure.

Demyttenaere et al (2009) reported a mean operative time of 65 minutes ( $\pm 15$  minutes standard deviation) and a mean length of hospital stay of 1 day (range, 0-6 days). One patient died of a drug overdose unrelated to the procedure a few months postoperative. Three symptomatic failures occurred; one in a patient with early postoperative vomiting and then recurrent heartburn, another in a patient with persistent symptoms at 1-month postoperative, and the final in a patient with excellent results for 2 weeks and the sudden reappearance of symptoms. In the first case, upper endoscopy revealed greater than 50% loss of fasteners and a loss of post-procedure valve geometry. Laparoscopic examination of the second case found a portion of the fundus tacked to the GE junction (wrap was  $<180^\circ$ ), and upper endoscopy in the third case showed broken fasteners through the fundoplication. All three patients underwent subsequent Nissen fundoplication.

Mean GORD-HRQL and symptom severity scores improved significantly from pre- to post-operative testing. Mean  $\pm$  SD GORD-HRQL was  $22 \pm 13$  before surgery and  $10 \pm 7$  3-months following surgery ( $P=0.0007$ ) while symptom score was  $34 \pm 14$  before surgery and  $17 \pm 15$  3-months following surgery ( $P=0.002$ ). However, only 45% of patients had  $>50\%$  improvement in HRQL scores. Medication use also dropped from 100% preoperatively to 68% (not statistically significant). Of the patients still taking PPIs, 31% had reduced their dosage by half. At a mean follow-up of 10 months, 45% of patients were satisfied with the EsophyX procedure, 25% of patients were neutral, and 30% of patients were dissatisfied.

Based on GORD-HRQL results in the study by Cadriere et al (2009) daily difficulty in swallowing without pain was reported in one patient and daily bloating or gassy feelings were reported in 7 patients. The prevalence of these symptoms at 2-years follow-up did not differ from baseline (whilst on PPIs) ( $P=0.6$ ). Overall GORD-HRQL scores improved significantly, by a median of 59% compared with baseline (whilst on PPIs) ( $P=0.004$ ). Sixty-four percent (9/14) of patients demonstrated clinically significant improvement in

their scores. Heartburn scores also improved from baseline (12-31) to 2-year follow-up (0-13). A score of 12 or less indicated heartburn elimination and this was apparent in 93% (13/14) of patients. Patient satisfaction was recorded in 86% of patients and one patient was recorded as being dissatisfied. Discontinuation of PPI therapy was sustained in 71% (10/14) of patients at 2-years postoperative. Also at 2-years follow-up, significantly more patients were able to consume certain known GORD-trigger foods without symptoms; these foods included citrus (P=0.049), deep-fried foods (P=0.018), spicy foods (P=0.001), carbonated drinks (P=0.006), coffee (P=0.001), caffeinated drinks (P=0.043), and alcohol (P=0.001). Significantly more patients were also able to eat late at night (P=0.022), exercise (P<0.001), and smoke (P=0.027).

Upper GI endoscopy found EsophyX-created funduplications had a median length of 3cm, which was 27% lower than that measured at the time of the procedure. There was no significant difference between median length at 2-years and 3-months follow-up (P=0.2), 6-months follow-up (P=0.2), or 12-months follow-up (P=0.6). Median transoral incisionless fundoplication circumference (200°) at 2-years follow-up was 14%, again lower than at the time of the procedure and there was no significant difference in circumference at 3-months (P=0.6), 6-months (P=0.3), or 12-months (P=0.2). Tight or moderate adherence of the funduplications was also observed, along with Hill grades I or II. Hiatal hernia was eliminated in 60% of patients, reduced in 20% of patients and a new hiatal hernia (2cm) was revealed in one patient. Oesophagitis was eliminated in 55% of patients and remained unchanged in five patients who had a fundoplication with loose (n=3) or moderate adherence (n=2).

Global assessment found 29% of patients were completely cured of GORD and 50% were in remission at 2-years follow-up. A remaining 21% of patients continued to experience symptoms of GORD. Although normal preoperative pH findings (both on and off PPIs) were more common in patients who were cured of GORD or who were in remission, compared with those still experiencing symptoms, there were no statistically significant differences seen.

## **2010 SUMMARY OF FINDINGS**

From the retrieved update studies EsophyX appears to offer an improvement in GORD symptoms, as well as a reduction/elimination in PPI therapy usage. Quality of life outcomes and patient satisfaction also appear to be improved following the procedure. Due to the low quality of the available literature (relatively small patient numbers and short durations of follow-up) this update's findings cannot be considered a reliable representation of the safety and efficacy of EsophyX.

## **2010 HEALTHPACT ACTION**

The results of EsophyX have so far been promising; with additional high quality studies, such as those comparing EsophyX with the current gold standard procedure, the potential benefits of EsophyX in patients suffering from GORD will be known. In particular, studies with large patient numbers and follow-up greater than 2-years are needed. Given the current limited evidence base and the potential for future follow-up studies it is recommended that EsophyX be monitored for a further 24 months.

## **2010 INCLUDED STUDIES**

Total number of studies	3
Level IV intervention evidence	3

## **2010 REFERENCES**

Repici A, Fumagalli U, Malesci A, Barbera R, Gambaro C, Rosati R. Endoluminal fundoplication (ELF) for GERD using EsophyX: a 12-months follow-up in a single-center experience. *J Gastrointest Surg* 2010; **14**(1):1-6.

Demyttenaere SV, Bergman S, Pham T, Anderson J, Dettorre R, Melvin WS, Mikami DJ. Transoral incisionless fundoplication for gastroesophageal reflux disease in an unselected patient population. *Surg Endosc* 2009 [Epub ahead of print].

Cadiere GB, Van Sante N, Graves JE, Gawlicka AK, Rajan A. Two-year results of a feasibility study on antireflux transoral incisionless fundoplication using EsophyX. *Surg Endosc* 2009; **23**(5): 957-964.

## **2010 SOURCES OF FURTHER INFORMATION**

Testoni PA, Corsetti M, Di Pietro S, Castellaneta AG, Vailati C, Masci E, Passaretti S. Effect of transoral incisionless fundoplication on symptoms, PPI use, and pH-impedance refluxes of GERD patients. *World J Surg* 2010; **34**(4): 750-757.