NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of endoscopic radiofrequency ablation for gastro-oesophageal reflux disease

Treating gastro-oesophageal reflux disease using electrical heat energy

Gastro-oesophageal reflux disease means that the acidic contents of the stomach are able to travel back up into the oesophagus (gullet). This is known as acid reflux and happens when the ring of muscle that holds the stomach contents in isn't working properly. It causes heartburn (a burning sensation or pain) and/or an acid taste in the mouth, and if severe can cause complications such as cough and problems with swallowing. In endoscopic radiofrequency ablation for gastro-oesophageal reflux disease, an endoscope (a tube containing a camera and other instruments) is inserted through the mouth and down the oesophagus. Electrically generated heat is used to form a scar beneath the lining of the oesophagus where it joins the stomach, with the aim of reducing the tendency of the stomach contents to reflux.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in January 2013 and updated in June 2013.

Procedure name

- Endoscopic radiofrequency ablation for gastro-oesophageal reflux disease.

Specialist societies

- Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland
- British Society of Gastroenterology.

Description

Indications and current treatment

Gastro-oesophageal reflux disease (GORD) is a common problem and is caused by a variety of conditions that disturb the sphincter function at the lower end of the oesophagus, such as hiatus hernia. Symptoms of GORD can be broadly grouped into those directly related to reflux episodes, such as heartburn, regurgitation, chest pain and nausea and those symptoms caused by complications of reflux disease, including dysphagia, respiratory difficulties, Barrett's oesophagus or oesophageal stricture.

Lifestyle modification and drug therapy are the standard treatments for patients with symptomatic GORD. Drug therapy includes antacids, alginates and acid-lowering agents such as H2-receptor antagonists and proton pump inhibitors (PPIs). Patients who have refractory symptoms, who develop complications despite medication or who develop intolerance to medication, may be considered for anti-reflux surgery (usually laparoscopic fundoplication). Fundoplication involves wrapping the uppermost part of the stomach around the distal oesophagus, by an open or laparoscopic approach. A number of alternative endoscopic techniques have also been used.

What the procedure involves

The aim of endoscopic radiofrequency ablation for GORD is to reduce symptoms. The mechanism of action is unclear.

Endoscopic radiofrequency ablation for GORD is usually performed with the patient under sedation. The distance to the gastro-oesophageal junction is measured endoscopically and a guidewire with a flexible tip is passed through the endoscope and left in the stomach; the endoscope is removed. A specially designed radiofrequency balloon catheter, consisting of an inflatable balloon-basket with 4 electrode needle sheaths, is inserted through the mouth over the guidewire and advanced to the gastro-oesophageal junction. The balloon is inflated to the diameter of the oesophagus and the electrodes are deployed to penetrate through the mucosa and deliver radiofrequency energy to the musculature of the lower oesophageal sphincter and the gastric cardia, creating small lesions. Several cycles of approximately 1 minute of radiofrequency energy are delivered. As the lesions heal, the tissue contracts and thickens, narrowing the oesophageal sphincter.

Outcome measures

- Reduction in reflux episodes as measured by 24-hour oesophageal pH monitoring (DeMeester scores include 6 different parameters: total per cent time pH less than 4.0, per cent time pH less than 4.0 in the upright period, per cent time pH less than 4.0 in the recumbent period, the total number of reflux episodes, the total number of reflux episodes longer than 5 minutes, and the duration of the longest reflux episode. A score of more than 14.7 is considered abnormal).

- Reduction in symptoms as measured by validated reflux questionnaires, such as the Reflux Disease Questionnaire.
- Reduction in medication usage.
- Improvement in quality of life; the gastro-oesophageal reflux disease health-related quality of life (GERD-HRQL) scale assesses patient symptoms and effects on daily living using 10 questions. Scores of 0–50 are recorded; from best to worst.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to endoscopic radiofrequency ablation for GORD. Searches were conducted of the following databases, covering the period from their commencement to 18 April 2013: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with gastro-oesophageal reflux disease.
Intervention/test	Endoscopic radiofrequency ablation.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on 2305 patients from 1 systematic review (including 2 randomised controlled trials [RCTs] and 18 cohort series), 2 additional RCTs, 1 non-randomised comparative study and 4 case series[1–8].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on endoscopic radiofrequency ablation for gastro-oesophageal reflux disease

Abbreviations used: GERD-HRQL, gastro-oesophageal reflux disease health-related quality of life; GORD, gastro-oesophageal reflux disease; NS, not significant; PPI, proton pump inhibitors; QOLRAD, quality of life in reflux and dyspepsia; RCT, randomised controlled trial; RF, radiofrequency.

Study details	Key efficacy findings	Key safety findings	Comments
Perry KA (2012)[1] **Systematic review and meta-analysis** USA Search date: November 2010 Study population: patients with GORD **n=1441 patients** (20 studies: 2 randomised sham-controlled trials [n=100] and 18 cohort series [n=1341]) Age: mean 48 years; Sex: 53% male Patient selection criteria: patients with GORD undergoing primary anti-reflux treatment; study design – RCT and cohort studies; availability of data on at least 2 of the following parameters: oesophageal manometry, pH study, quality of life indices, and medication usage. Studies were excluded if they included children, or if the reported follow-up interval was <3 months. Preliminary studies containing patient populations that were subsequently reported in larger series with longer follow-up intervals were also excluded. Technique: RF delivery to the gastro-oesophageal junction using the Stretta system (Mederi Therapeutics Inc., USA) **Follow-up: mean 17 months (range 4–53)** Conflict of interest/source of funding: supported by an unrestricted research grant from Mederi Therapeutics Inc. The authors declared no conflicts of interest.	Number of patients analysed: **1441** **Comparison of baseline and post-treatment subjective and objective outcome measures** See table below. The most common complications were gastroparesis and ulcerative oesophagitis (numbers not reported). The authors noted that there were reports of oesophageal perforation associated with this procedure at its inception but they have not been reported since. In 2 cohort studies of 109 and 83 patients respectively, 75% and 86% of patients were medication free at 48 months. In 1 cohort study of 32 patients with mean follow-up of 53 months, 15% (2/13) responders were off PPI at follow-up; 59% of patients needed anti-reflux surgery about 6 months after the RF ablation (the authors noted that this was in an unselected population).		**Study design issues**: • Subjective outcome assessments included heartburn and patient satisfaction scores calculated on a 5-point Likert scale, disease specific quality-of-life scores (GERD-HRQL and QOLRAD) and global quality-of-life assessment (SF-36 and SF-12). Objective treatment outcomes included Johnson-DeMeester score (a cumulative score with 6 different parameters, lower scores indicate less oesophageal acid exposure), oesophageal acid exposure time, and mean lower oesophagus sphincter pressure. • Results from at least 4 studies were pooled and included in the meta-analysis. • Methodology and definition of criteria for some variables varied between studies. • Heterogeneity of the study population across the reports may influence the interpretation of the pooled results. • Excluded studies were not listed.

Outcome variable	Studies (n)	Patients (n)	Mean follow-up (months)	Base-line	After procedure	p value
GERD-HRQL score (lower scores better)	9	433	19.8	26.11	9.25	0.0001
QOLRAD score (higher scores better)	4	250	25.2	3.30	4.97	0.0010
SF-36 score (physical)	6	299	9.5	36.45	46.12	0.0001
SF-36 score (mental)	5	264	10.0	46.79	55.16	0.0015
Heartburn score	9	525	24.1	3.55	1.19	0.0001
Satisfaction score	5	366	21.9	1.43	4.07	0.0006
Oesophageal acid exposure (% pH<4)	11	364	11.9	10.29	6.51	0.0003
Johnson-DeMeester score	7	267	13.1	44.37	28.53	0.0074
Lower oesophagus sphincter pressure (mmHg)	7	263	8.7	16.54	20.24	0.0302

Abbreviations used: GERD-HRQL, gastro-oesophageal reflux disease health-related quality of life; GORD, gastro-oesophageal reflux disease; NS, not significant; PPI, proton pump inhibitors; QOLRAD, quality of life in reflux and dyspepsia; RCT, randomised controlled trial; RF, radiofrequency.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Arts J (2012)[2]

RCT (crossover design)

Belgium

Recruitment period: not reported

Study population: patients with GORD

n=22 (11 active vs 11 sham)

Age: mean 47 years; Sex: 23% (5/22) male

Patient selection criteria: complete or partial response to high-dose PPI; long-standing history of GORD with typical symptoms and pathological oesophageal pH monitoring (>4% of time pH<4). Exclusion criteria included age <18 years, large hiatal hernia (>3 cm), Barrett's oesophagus or history of high-grade erosive oesophagitis.

Technique: Stretta system was used; 1 procedure was done with the patient under general anaesthesia; the others were done under sedation. After the procedure, endoscopy was done to assess haemostasis and to detect complications.

Follow-up: 6 months

Conflict of interest/source of funding: none</td>
<td>Number of patients analysed: 22 (11 vs 11)

RF ablation procedure was incomplete in 3 patients because of difficulty with needle deployment.

Gastro-oesophageal junction compliance (ml/mmHg)
<table>
<tr><th></th><th>Baseline</th><th>3 months</th></tr>
<tr><td>Sham</td><td>14.0±5.3</td><td>13.3±4.3
p=NS</td></tr>
<tr><td>Active</td><td>17.8±3.6</td><td>7.4±3.4
p<0.05</td></tr>
</table>
Compliance was normalised to baseline levels after administration of sildenafil (an oesophageal smooth muscle relaxant), arguing against fibrosis as an underlying mechanism.
Symptom scores (lower scores better)
<table>
<tr><th></th><th>Baseline</th><th>3 months</th><th>6 months</th></tr>
<tr><td>Active/ sham</td><td>14.7±1.5</td><td>8.3±1.9
p<0.005</td><td>7.8±2.1</td></tr>
<tr><td>Sham/ active</td><td>16.1±2.5</td><td>15.6±2.2
p=NS</td><td>7.2±1.6
p<0.05</td></tr>
</table>
Selected SF-36 scores before and after treatment (range 0 to 100, higher scores better)
<table>
<tr><th></th><th>Physical functioning</th><th>Bodily pain</th><th>General health</th></tr>
<tr><td>Baseline for active group</td><td>56.7±13.4</td><td>24.0± 4.3</td><td>43.6±5.6</td></tr>
<tr><td>3 months after active treatment</td><td>73.8±9.3</td><td>49.5± 9.5*</td><td>61.6±7.1</td></tr>
<tr><td>6 months after active treatment</td><td>65.6±12.0</td><td>52.3± 13.6</td><td>55.0±8.5</td></tr>
<tr><td>Baseline for sham group</td><td>57.5±6.4</td><td>25.6± 5.9</td><td>31.4±8.2</td></tr>
<tr><td>3 months after sham procedure</td><td>76.1±5.6</td><td>31.9± 4.4</td><td>42.7±8.1</td></tr>
<tr><td>3 months after cross-over to active treatment</td><td>80.5±6.0**</td><td>69.2± 7.8**</td><td>61.0±9.6*</td></tr>
</table>
*p<0.05, **p<0.005 compared with baseline</td>
<td>Transient retrosternal pain that did not need analgesics was reported by several patients (lasting up to 5 days)

Throat ache was reported by 3 patients after active treatment and by 2 patients after the sham procedure.</td>
<td>This trial was not included in the systematic review by Perry et al., 2012.

Study design issues:
• Patients were randomised in a double-blind manner into 2 groups: the first group had RF ablation first and a sham procedure 3 months later. The second group had a sham procedure followed by active treatment 3 months later. Patients were evaluated by investigators who were unaware of treatment allocation.
• The sham procedure was performed in the same way as the active treatment but the needle electrodes were not deployed and the catheter was not connected to the RF generator.
• The primary outcome was the change in compliance of the gastro-oesophageal junction.
• Patients were asked to try and stop PPI therapy 3 weeks after the procedure.
• Reflux score included 14 different reflux symptoms scored from 0 to 3 (0=absent; 3=interfering with daily activity).
• Intention to treat analysis.
• Reflux evaluation did not include impedance monitoring.</td>
</tr>
</table>

Abbreviations used: GERD-HRQL, gastro-oesophageal reflux disease health-related quality of life; GORD, gastro-oesophageal reflux disease; NS, not significant; PPI, proton pump inhibitors; QOLRAD, quality of life in reflux and dyspepsia; RCT, randomised controlled trial; RF, radiofrequency.

Study details	Key efficacy findings	Key safety findings	Comments
	Follow-up endoscopy (at 3 and 6 months follow-up) No significant changes occurred in the number of patients with erosive oesophagitis or in the severity of oesophagitis. ***24-hour pH monitoring*** There were no significant changes in oesophageal acid exposure after 3 or 6 months. ***Medication use (number of PPI tablets/month)*** Baseline / 3 months / 6 months Active/ sham: 32.0±4.8 / 33.3±2.9 p=NS / 32.5±7.0 p=NS Sham/ active: 32.1±3.5 / 24.0±3.0 p=NS / 24.1±5.7 p=NS Data are shown as mean ± standard error		

Abbreviations used: GERD-HRQL, gastro-oesophageal reflux disease health-related quality of life; GORD, gastro-oesophageal reflux disease; NS, not significant; PPI, proton pump inhibitors; QOLRAD, quality of life in reflux and dyspepsia; RCT, randomised controlled trial; RF, radiofrequency.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Coron E (2008)[3]

RCT (multicentre)

France, Belgium
Recruitment period: 2003–6

Study population: patients with chronic GORD

n=43 (23 RF ablation versus 20 PPI alone)

Age: mean 48 years; Sex: 70% (30/43) male

Patient selection criteria: age >18 years; diagnosis of GORD established by either 24-hour oesophageal pH monitoring showing an abnormal oesophageal acid exposure and/or upper gastrointestinal endoscopy showing oesophagitis (grade A or B in Los Angeles classification); typical symptoms of GORD at least 3 times a week in the absence of PPI therapy; adequate symptom relief obtained with PPIs but needing maintenance with at least standard dose. Exclusion criteria included Barrett’s oesophagus >3 cm and/or with dysplasia and/or previously treated; hiatus hernia >3 cm; oesophagitis grade C or D; oesophageal stricture or achalasia; history of oesophageal or gastric surgery; gastric or oesophageal varices.

Technique: Stretta system was used (Curon Medical, USA). All patients were treated under general anaesthesia. After the procedure, endoscopy was done to verify the absence of complications.

Follow-up: 12 months

Conflict of interest/source of funding: the work was supported in part by the Société Nationale Francaise de Gastro-Entérologie, INSERM and CHU of Nantes. The study was conducted</td>
<td>Number of patients analysed: 43 (23 versus 20)

Proportion of patients who could stop or decrease PPI use to <50% of effective dose:
<table>
<tr><td>Follow-up</td><td>RF ablation</td><td>control</td><td>p value</td></tr>
<tr><td colspan="4">Intention to treat analysis</td></tr>
<tr><td>6 months</td><td>78% (18/23)</td><td>40% (8/20)</td><td>0.01</td></tr>
<tr><td>12 months</td><td>56% (13/23)</td><td>35% (7/20)</td><td>0.16</td></tr>
<tr><td colspan="4">Per protocol analysis</td></tr>
<tr><td>6 months</td><td>90% (18/20)</td><td>50% (8/16)</td><td>0.01</td></tr>
<tr><td>12 months</td><td>65% (13/20)</td><td>38% (6/16)</td><td>0.10</td></tr>
</table>
13% (3/23) and 17.4% (4/23) of patients in the RF group at 6 and 12 months respectively were able to stop PPI therapy completely versus none of the control patients.

Secondary end points (6 months follow-up, per protocol analysis, means ± standard deviation)
<table>
<tr><td></td><td>RF ablation</td><td>control</td><td>p value</td></tr>
<tr><td>PPI dose required to achieve symptom control (mg)</td><td>12±11</td><td>30±19</td><td>0.01</td></tr>
<tr><td>Symptom frequency <3 per week</td><td>80% (16/20)</td><td>40% (6/15)</td><td>0.01</td></tr>
<tr><td>Heartburn score</td><td>2.1±1.0</td><td>2.4±1.4</td><td>0.47</td></tr>
<tr><td>Regurgitation score</td><td>1.3±0.6</td><td>2.2±1.3</td><td>0.01</td></tr>
<tr><td>Epigastric burning score</td><td>1.4±0.9</td><td>2.5±1.4</td><td>0.01</td></tr>
<tr><td>SF-36 physical</td><td>48±8</td><td>49±7</td><td>0.81</td></tr>
<tr><td>SF-36 mental</td><td>51±9</td><td>45±12</td><td>0.20</td></tr>
<tr><td>REFLUX-QUAL global score</td><td>75±21</td><td>68±21</td><td>0.43</td></tr>
<tr><td>Abnormal oesophageal acid exposure</td><td>94% (17/18)</td><td>75% (9/12)</td><td>0.27</td></tr>
<tr><td>Oesophagitis (%) (diagnosed by endoscopy)</td><td>53% (10/19)</td><td>54% (7/13)</td><td>0.97</td></tr>
</table>
</td>
<td>There were no reports of aspiration, perforation, bleeding that needed transfusion, or death.

Adverse events in the RF ablation group:
• Transient abdominal pain or epigastric discomfort=17.4% (4/23)
• Transient swallowing pain=4.4% (1/23)
• Transient fever=4.4% (1/23)</td>
<td>This trial was not included in the systematic review by Perry et al., 2012.

Follow-up issues:
• After randomisation, 6 patients in the control group were excluded (4 were lost to follow-up); 3 patients in the treatment group were excluded (2 withdrew consent and 1 patient had a car accident).

Study design issues:
• A sample size of 100 patients was calculated to detect a difference of 30% on the primary end point (possibility for patient to stop or decrease PPI use to <50% effective dose during the last 6 weeks); the study was interrupted in 2006 because the manufacturer decided to stop the development and commercialisation of the RF system.
• There was a 6 to 12 week run-in phase before randomisation, during which patients with highly variable symptoms or those with symptoms controlled by half-dose PPI were excluded.
• The REFLUX-QUAL is a French validated questionnaire with scores ranging from 0 (worst) to 100 (best).</td>
</tr>
</table>

Abbreviations used: GERD-HRQL, gastro-oesophageal reflux disease health-related quality of life; GORD, gastro-oesophageal reflux disease; NS, not significant; PPI, proton pump inhibitors; QOLRAD, quality of life in reflux and dyspepsia; RCT, randomised controlled trial; RF, radiofrequency.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>independently of Curon Ltd with no interference in the trial design or analysis of results.</td>
<td>
Secondary end points (12 months follow-up, per protocol analysis, means ± standard deviation)
<table>
<tr><th></th><th>RF ablation</th><th>control</th><th>p value</th></tr>
<tr><td>PPI dose required to achieve symptom control (mg)</td><td>16±14</td><td>37±30</td><td>0.05</td></tr>
<tr><td>Symptom frequency <3 per week</td><td>69% (11/20)</td><td>62% (8/14)</td><td>0.71</td></tr>
<tr><td>Heartburn score</td><td>1.7±0.8</td><td>2.3±1.5</td><td>0.42</td></tr>
<tr><td>Regurgitation score</td><td>1.2±0.4</td><td>1.7±1.4</td><td>0.58</td></tr>
<tr><td>Epigastric burning score</td><td>1.3±0.6</td><td>2.0±1.4</td><td>0.08</td></tr>
<tr><td>SF-36 physical</td><td>53±7</td><td>40±10</td><td>0.50</td></tr>
<tr><td>SF-36 mental</td><td>51±9</td><td>50±7</td><td>0.30</td></tr>
<tr><td>REFLUX-QUAL global score</td><td>84±9</td><td>77±18</td><td>0.24</td></tr>
</table>
</td>
<td></td>
<td>Study population issues:
There were no statistically significant differences between the 2 patient groups at baseline.</td>
</tr>
</table>

Abbreviations used: GERD-HRQL, gastro-oesophageal reflux disease health-related quality of life; GORD, gastro-oesophageal reflux disease; NS, not significant; PPI, proton pump inhibitors; QOLRAD, quality of life in reflux and dyspepsia; RCT, randomised controlled trial; RF, radiofrequency.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Jeansonne L (2009)[4]

Non-randomised comparative study

USA
Recruitment period: 2002–6

Study population: patients with GORD

n=126 (68 RF ablation versus 58 endoluminal full-thickness plication)

Age: mean 49 years (RF ablation)
Sex: not reported

Patient selection criteria: contraindications to both procedures included large paraoesophageal hernia, oesophagitis, and stricture.

Technique: Stretta system was used (Curon Medical, USA).

Follow-up: mean 5 months for RF ablation group and 8 months for plication group

Conflict of interest/source of funding: none</td>
<td>Number of patients analysed: 64 (41 versus 23) – calculated by IP analyst (no absolute numbers are given in the paper)

<table>
<tr><th></th><th colspan="2">RF ablation</th><th colspan="2">Plication</th></tr>
<tr><td></td><td>Base-line</td><td>Follow-up</td><td>Base-line</td><td>Follow-up</td></tr>
<tr><td>PPI use</td><td>84%</td><td>50%
p=0.01</td><td>95%</td><td>43%
p=0.01</td></tr>
<tr><td>Moderate to severe heart-burn</td><td>55%</td><td>22%
p<0.01</td><td>53%</td><td>43%
p=0.3</td></tr>
<tr><td>Percentage of time pH<4</td><td>10.8%</td><td>9.1%
p=NS</td><td>10.0%</td><td>6.1%
p=0.05</td></tr>
<tr><td>Moderate to severe scores for dysphagia</td><td>17.4%</td><td>14.6%
p=0.04</td><td>28.6%</td><td>0%
p=0.01</td></tr>
<tr><td>Moderate to severe scores for regurgitation</td><td>48%*</td><td>19%*
p=not reported</td><td>62.5%</td><td>18.8%
p=0.02</td></tr>
<tr><td>Moderate to severe scores for voice symptoms</td><td>29.8%</td><td>14.6%
p=0.04</td><td>35.7%</td><td>18.8%
p=0.01</td></tr>
<tr><td>Moderate to severe scores for cough</td><td>32.6%</td><td>12.2%
p=0.01</td><td>15%*</td><td>5%*
p=NS</td></tr>
</table>
* estimated from graphical presentation

3 patients (4%) in the RF ablation group and 3 patients (5%) in the plication group underwent laparoscopic Nissen fundoplication for refractory symptoms an average of 11.4 months after treatment.</td>
<td></td>
<td>This trial was not included in the systematic review by Perry et al., 2012.

Follow-up issues:
• Follow-up data were obtained for 51% of patients (60% versus 40%).

Study design issues:
• For the first 2 years of the study, only RF was available. For the remainder of the study period, the choice of treatment was based on patient preference, the surgeon’s judgement and anatomic favourability.
• After both procedures, patients were instructed to continue their anti-reflux medication for 7 days.

Study population issues:
• The 2 groups were similar with regard to age, sex and body mass index. In the RF group, 15% of patients had a history of previous fundoplication compared with 9% in the plication group.</td>
</tr>
</table>

Abbreviations used: GERD-HRQL, gastro-oesophageal reflux disease health-related quality of life; GORD, gastro-oesophageal reflux disease; NS, not significant; PPI, proton pump inhibitors; QOLRAD, quality of life in reflux and dyspepsia; RCT, randomised controlled trial; RF, radiofrequency.

Study details	Key efficacy findings	Key safety findings	Comments
Dughera L (2011)[5] **Case series (prospective)** Italy Recruitment period: 2002–7 Study population: patients with GORD **n=56** Age: mean 42 years Sex: 64% (36/56) male Patient selection criteria: age >18 years; heartburn or acid regurgitation quite well responsive to daily PPI medication; 24-hour pH study (off medication) showing abnormal oesophageal acid exposure (≥4%) and a DeMeester score >14.7; oesophageal manometry showing normal peristalsis and sphincter relaxation and lower oesophageal sphincter pressure below 10 mmHg and above 5 mmHg; no low-grade oesophagitis; no hiatal hernia or not longer than 2 cm; no Barrett's oesophagus. Technique: Stretta system was used; all procedures were done on an outpatient day-hospital basis using sedation. Oesophagogastroduodenoscopy was done immediately after the procedure to evaluate the RF-induced lesion placement. **Follow-up: 48 months** Conflict of interest/source of funding: none	Number of patients analysed: **56** ***Mean symptom and quality of life scores*** | | Baseline | 24 months | 48 months | |---|---|---|---| | Heartburn score | 8 | 5* | 4* | | GERD-HRQL | 29 | 15** | 17** | | SF36 mental | 40 | 48# | 49# | | SF36 physical | 50 | 55* | 58* | All numbers have been estimated from a graph. *p<0.001, **p<0.003, #p<0.05 Symptom and quality of life scores were significantly improved in 92.8% (52/56) of patients at 24 and 48 months. ***Mean lower oesophageal sphincter pressure (mmHg)*** • Baseline=8.44 (95% CI: 7.2 to 11.7) • 24 months=9.5 (95% CI: 7.8 to 10.2) • 48 months=9.1 (95% CI: 6.9 to 9.2) At 48-month follow-up endoscopy, none of the treated patients showed oesophagitis or Barrett's oesophagus At 48 months, 72% (41/56) of patients were completely off PPIs; 14% of patients used occasional oral antacids.	There were no perforations, mucosal lacerations, bleeding episodes needing transfusion, or deaths after the procedure. • Chest pain=26.7% (15/56) • Mild fever=7.1% (4/56) • Transient nausea and/or vomiting=10.7% (6/56) • Transient dysphagia=7.1% (4/56) • Prolonged gastroparesis=1.7% (1/56) (complete resolution within 8 weeks)	**Follow-up issues**: • An additional 13 patients were treated by RF ablation but were excluded from the analysis (9 patients had not reached the 48-month follow-up visit, 2 patients were lost to follow-up and 2 patients had laparoscopic anti-reflux surgery after RF ablation failed within 6 weeks. **Study design issues**: • The primary outcomes were heartburn (using a 6-point Likert scale, ranging from 0 [no symptoms] to 5 [incapacitating symptoms]), GERD-HRQL (using a 6-point Likert scale) and general quality of life using the 36-item SF Health Survey (higher scores for better function). • All patients continued their current PPI regimen for 30 days and then discontinued all antacid medications.

Abbreviations used: GERD-HRQL, gastro-oesophageal reflux disease health-related quality of life; GORD, gastro-oesophageal reflux disease; NS, not significant; PPI, proton pump inhibitors; QOLRAD, quality of life in reflux and dyspepsia; RCT, randomised controlled trial; RF, radiofrequency.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Gao X (2011)[6]

Case series (prospective)

China

Recruitment period: 2006 – 8

Study population: patients with GORD presenting with mainly respiratory symptoms such as wheezing, chronic cough or hoarseness

n=505

Age: mean 48 years (range 21–77)
Sex: 52% (264/505) males

Patient selection criteria: exclusion criteria were significant ineffective oesophageal motility associated with GORD, poor surgical candidates, severe dysphagia, or previous oesophageal or gastric surgery. Patients with hiatal hernia >2 cm in diameter and oesophagitis exceeding grade 3 were also excluded. All patients had partial symptoms while on medication, or were unwilling to accept lifelong medication or refused laparoscopic anti-reflux surgery.

Technique: Stretta system was used, most patients (n=501) were treated under sedation.

Follow-up: 12 months

Conflict of interest/source of funding: none</td>
<td>Number of patients analysed: 505

Symptom scores at baseline and 12 month follow-up (mean ± standard deviation)
<table>
<tr><th></th><th>Baseline</th><th>12 months</th><th>p value</th></tr>
<tr><td>Heartburn</td><td>5.31±1.56</td><td>1.79±0.92</td><td><0.01</td></tr>
<tr><td>Regurgitation</td><td>5.02±1.34</td><td>1.64±0.97</td><td><0.01</td></tr>
<tr><td>Cough</td><td>6.77±1.31</td><td>2.85±1.36</td><td><0.01</td></tr>
<tr><td>Wheezing</td><td>7.83±1.79</td><td>3.07±1.82</td><td><0.01</td></tr>
<tr><td>Hoarseness</td><td>5.13±1.48</td><td>1.81±0.93</td><td><0.01</td></tr>
</table>
Drug doses were reduced significantly after RF ablation for 71.7% (362/505) of patients.

6.9% (35/505) of patients had recurrence of symptoms; RF treatment was repeated in 6 patients and another 7 proceeded to laparoscopic fundoplication.</td>
<td>There were no serious mucosal lacerations, massive bleeding or death.

‘Minor’ complications:
Chest pain=21.0% (106/505)
Mild fever (<38°C)=17.0% (86/505)
Transient nausea and/or vomiting=19.2% (97/505)
Transient dysphagia=8.3% (42/505)</td>
<td>Study design issues:
The Reflux Diagnostic Questionnaire uses a 6-point scale ranging from 0 (best) to 5 (worst) to assess the frequency and severity of symptoms.</td>
</tr>
</table>

Abbreviations used: GERD-HRQL, gastro-oesophageal reflux disease health-related quality of life; GORD, gastro-oesophageal reflux disease; NS, not significant; PPI, proton pump inhibitors; QOLRAD, quality of life in reflux and dyspepsia; RCT, randomised controlled trial; RF, radiofrequency.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Liu H-F (2011)[7]

Case series (prospective)

China
Recruitment period: 2007–10

Study population: patients with GORD

n=90

Age: mean 51 years (range 31–72)
Sex: 63% (57/90) male

Patient selection criteria: age >18 and <80 years; diagnosis of GORD confirmed by finding erosive oesophagitis at upper endoscopy or abnormal acid contact time detected at ambulatory oesophageal pH testing. Exclusion criteria were achalasia, sliding hiatal hernia >2 cm, collagen vascular disease, severe uncontrolled medical illness, and pregnancy. All patients had significant GORD with persistent symptoms of heartburn and regurgitation despite taking daily PPIs.

Technique: Stretta system was used (Curon Medical Inc., USA) in an outpatient endoscopy unit. All procedures were done with sedation. Diagnostic endoscopy was repeated after the procedure to check for complications.

Follow-up: 12 months

Conflict of interest/source of funding: not reported</td>
<td>Number of patients analysed: 90

Symptom and quality of life scores (mean ± standard deviation) at baseline and after RF ablation

<table>
<tr><th>Clinical parameter</th><th>Baseline</th><th>6 months</th><th>12 months</th><th>p value</th></tr>
<tr><td>GERD-HRQL</td><td>25.6±9.0</td><td>7.3±4.1</td><td>8.1±3.9</td><td><0.01</td></tr>
<tr><td>Heartburn</td><td>3.3±1.3</td><td>1.0±0.9</td><td>1.2±1.1</td><td><0.01</td></tr>
<tr><td>Satisfaction</td><td>1.4±1.1</td><td>4.3±1.3</td><td>4.0±0.9</td><td><0.01</td></tr>
<tr><td>Percentage of patients without PPI</td><td>0</td><td>78.9</td><td>76.7</td><td><0.05</td></tr>
</table>

Improvement in endoscopic grade of oesophagitis
80.5% (33/41) of patients had an improvement in endoscopic grade of oesophagitis at the 6-month follow-up; 80.5% of patients had no erosions and 19.5% of patients had mild erosive disease (grade A).</td>
<td>‘Minor’ complications:
• Dyspepsia=5.6% (5/90)
• Transient chest pain=10.0% (9/90)
• Superficial mucosal injury=2.2% (2/90)
• Mucosal bleeding=3.3% (3/90)
• Low-grade fever=2.2% (2/90)

All complications resolved within 1 week; there were no serious complications noted after the procedure.</td>
<td>Follow-up issues:
• The paper does not state how many patients were assessed at 6 and 12 months (endoscopy results were described for only 41 patients at 6 months).

Study design issues:
• All medication was maintained for 6 to 8 weeks after the procedure to maintain baseline and allow time for complete healing.
• The GERD-HRQL questionnaire had a score ranging from 0–50, with scores less than 10 considered normal.
• Patient satisfaction was measured on a scale of 0–5, with higher scores indicating better satisfaction (no details of validation available.
• Medication usage was assessed at baseline and at 6 months with the assistance of patient diaries.</td>
</tr>
</table>

Abbreviations used: GERD-HRQL, gastro-oesophageal reflux disease health-related quality of life; GORD, gastro-oesophageal reflux disease; NS, not significant; PPI, proton pump inhibitors; QOLRAD, quality of life in reflux and dyspepsia; RCT, randomised controlled trial; RF, radiofrequency.

Study details	Key efficacy findings	Key safety findings	Comments
Madan A K (2006)[8] **Case series** (Retrospective review of the US Food and Drug Administration Manufacturer and User Facility Device Experience Database [MAUDE] up to April 2005.) USA Study period: up to April 2005 Study population: Patients with GORD (not otherwise defined). **n=22 (RF ablation)** Age: not reported Sex: not reported Inclusion criteria: Not reported Technique: Stretta system **Follow-up: not reported** Conflict of interest: not reported.	Efficacy outcomes were not reported on.	**Complications** There were 3 deaths related to RF ablation for GORD in the database, and 22 overall complications. In the group as a whole (n=50 endoscopic procedures reporting an adverse event) 64% of complications required hospitalisation and 16 patients underwent a subsequent procedure, including repeat procedure in 9 patients. Reported or suggested perforation occurred in 38% of the adverse events (the paper does not state how many were related to RF ablation). It is difficult to estimate the incidence rate for these complications as the denominator 'number of procedures undertaken' is hard to determine. Assuming 6000 RF ablation procedures had been undertaken to the date of analysis (based on manufacturer sales), a minimal complication rate was about 0.4% after RF ablation.	This study was included in the original overview; it was not included in the systematic review by Perry et al., 2012. **Study design issues:** • Duplicate reports of the same incident were excluded. • The study examined adverse events for a range of endoscopic interventions for GORD including endoscopic suturing, and injection of bulking agent. Many outcomes were not reported separately for each intervention. • Because of the nature of the database, cause and effect relationships cannot be ascertained. • The MAUDE database is not mandatory and there may have been under-reporting of complications. • Full clinical information (i.e. case history, patient risk factors, mitigating circumstances, or other technical problems) is not recorded for each patient / incident.

Efficacy

Quality of life

A systematic review of 20 studies including 1441 patients reported the mean GERD-HRQL score in 9 studies (n=433 patients), which improved from 26.1 at baseline to 9.3 after treatment (p=0.0001, mean follow-up=20 months)[1]. In the same review, 4 studies (n=250 patients) reported quality of life using a different scale (quality of life in reflux and dyspepsia [QOLRAD]); the mean score improved from 3.3 at baseline to 5.0 at mean follow-up of 25 months (p=0.001). Six studies with 299 patients reported the mean SF-36 (physical) score improved from 36 to 46 points at mean follow-up of 10 months (p=0.0001) and 5 studies (n=264 patients) reported the mean SF-36 (mental) score improved from 47 to 55 at mean follow-up of 10 months (p=0.0015).

An RCT of 43 patients treated by endoscopic radiofrequency (RF) ablation or PPI therapy alone reported mean SF-36 (physical) scores of 53 and 40 respectively at 12 months' follow-up (p=0.50); SF-36 (mental) scores were 51 and 50 respectively (p=0.30)[3].

Symptoms

The systematic review of 20 studies reported a pooled heartburn score from 9 studies (n=525) of 3.6 at baseline and 1.2 at mean follow-up of 24 months (p=0.0001; lower scores indicate less severe symptoms)[1].

A crossover RCT of 22 patients comparing RF ablation against sham reported a significant improvement in symptom score compared with baseline in the active treatment group (from 14.7 to 8.3, p<0.005) but not in the sham group (from 16.1 to 15.6, p=not significant). When patients in the sham group were subsequently treated by RF ablation, the symptom score significantly improved to 7.2 (p<0.05) at 3-month follow-up [2].

The RCT of 43 patients treated by endoscopic RF ablation or PPI therapy alone reported symptoms fewer than 3 times a week in 80% (16/20) and 40% (6/15) of patients respectively at 6 months' follow-up (p=0.01)[3]. Individual scores for heartburn, regurgitation and epigastric burning were 2.1, 1.3 and 1.4 respectively in the RF treatment group and 2.4, 2.2 and 2.5 in the control group (p=0.47, 0.01 and 0.01 respectively). At 12 months' follow-up, 69% (11/20) of patients in the RF ablation group had symptoms fewer than 3 times a week compared with 62% (8/14) of patients in the control group (p=0.71). There were no statistically significant differences in the individual symptom scores.

A non-randomised comparative study of 126 patients treated by RF ablation or endoluminal full-thickness plication reported a decrease in the proportion of patients with moderate-to-severe heartburn from 55% to 22% (p<0.01) and from 53% to 43% (p=0.3) respectively at mean follow-up of 5 and 8 months. The

proportion of patients with moderate-to-severe dysphagia decreased from 17% to 15% (p=0.04) and from 29% to 0% (p=0.01) respectively[4].

Medication usage

The crossover RCT of 22 patients comparing RF ablation against sham reported no significant change in medication use from baseline in either group at 6 months' follow-up[2]. The RCT of 43 patients reported that 78% (18/23) and 56% (13/23) of patients treated by RF ablation could stop or decrease PPI use to less than 50% of the effective dose at 6 and 12 months respectively compared with 40% (8/20) and 35% (7/20) of patients treated by PPI therapy alone (p=0.01 and p=0.16)[3]. The same study reported that 13% (3/23) and 17% (4/23) of patients in the RF group at 6 and 12 months respectively were able to stop PPI therapy completely compared with none of the control patients.

The non-randomised comparative study of 126 patients reported PPI use at baseline in 84% of patients treated by RF ablation and 95% of patients treated by endoluminal full-thickness plication; these proportions decreased to 50% and 43% respectively at mean follow-up of 5 and 8 months (p=0.01 for both)[4].

Oesophageal acid exposure

The systematic review reported oesophageal acid exposure from 11 studies including 364 patients. The mean percentage of time that pH was less than 4 decreased from 10% at baseline to 7% (p=0.0003) at mean follow-up of 12 months[1]. The crossover RCT of 22 patients reported that there were no significant changes in oesophageal acid exposure after 3 or 6 months[2]. The RCT of 43 patients reported abnormal oesophageal acid exposure in 94% (17/18) of patients treated by RF ablation and in 75% (9/12) of patients treated by PPI therapy alone at 6 months' follow-up (p=0.27)[3].

Respiratory symptoms

The non-randomised comparative study of 126 patients reported moderate-to-severe cough at baseline in 33% of patients treated by RF ablation and 15% of patients treated by endoluminal full-thickness plication; these proportions decreased to 12% and 5% respectively at mean follow-up of 5 and 8 months (p=0.01 and p=not significant)[4]. A case series of 505 patients reported statistically significant reductions in symptom scores for cough, wheezing and hoarseness from 6.8, 7.8 and 5.1 respectively at baseline to 2.9, 3.1 and 1.8 at 12 months' follow-up (p<0.01 for all 3)[6].

Safety

Mucosal injury

Superficial mucosal injury was reported in 2% (2/90) of patients in a case series of 90 patients[7]. Mucosal bleeding was reported in 3% (3/90) of patients in the same study.

Chest pain

Transient chest pain was reported in 10% (9/90), 21% (106/505) and 27% (15/56) of patients in 3 case series[5,6,7].

Dysphagia

Transient dysphagia was reported in 7% (4/56) and 8% (42/505) of patients in 2 case series[5,6].

Gastroparesis

Prolonged gastroparesis, which resolved within 8 weeks, was reported in 1 patient in a case series of 56 patients[5].

Nausea and vomiting

Transient nausea and/or vomiting was reported in 11% (6/56) and 19% (97/505) of patients in 2 case series[5,6].

Other

One case series reported solely on adverse events after endoscopic interventions for GORD[8]. Among patients who underwent RF ablation, 3 deaths and 22 overall complications were reported. However, it was difficult to establish the actual rate, as the denominator 'number of procedures performed' was not stated precisely.

Validity and generalisability of the studies

- A systematic review has been summarised that includes studies published between 2000 and 2010[1]. This includes all the studies previously summarised in the original overview (for interventional procedures guidance 292), with the exception of Madan et al. (2006)[8]. The remaining studies now described in table 2 were not included in the systematic review, mainly because they were published at a later date.
- The systematic review included 2 RCTs of 64 and 36 patients respectively and a further 2 small RCTs have been described in table 2; 3 of these trials were sham-controlled.
- The systematic review noted that there were reports of oesophageal perforation associated with this procedure at its inception but they have not been reported since. None of the new studies included in table 2 report this as a complication.

- The systematic review meta-analysis is limited by differences in methodology and definition of criteria for some variables between studies. Heterogeneity of the study populations may also influence interpretation of the pooled results.
- The non-randomised comparative study was not sham-controlled and the choice of treatment was made by the patient and physician[4]. It also had a relatively short follow-up period for the group of patients treated by RF ablation (5 months).
- Some of the improvements reported in non-blinded studies may be caused by a placebo effect.
- Most of the studies reported subjective symptom scores that may be subject to bias.
- Patient selection criteria varied between studies.
- The systematic review reported data with a mean follow-up of 17 months (range 4 to 53 months). The 2 RCTs presented in table 2 report follow-up to 6 and 12 months respectively; 1 case series reported follow-up longer than 12 months, which reported follow-up to 48 months[5].
- In 1 case series of 56 patients, an additional 2 patients were excluded from the analysis because they had laparoscopic anti-reflux surgery after RF ablation failed within 6 weeks[5].

Existing assessments of this procedure

The Australian Safety and Efficacy Register of New Interventional Procedures – Surgical reviewed the evidence on a range of endoscopic treatment modalities for the treatment of GORD in a report published in August 2006[9].

The following section relates to the evidence for endoscopic radiofrequency ablation.

‘Limited evidence suggested that in a select group of patients the Stretta Procedure produces improvements in symptoms and quality of life that are comparable to laparoscopic fundoplication and superior to sham treatment. Another intervention is generally required in up to 10% of patients two years after treatment. The main advantage of the Stretta Procedure is that it causes fewer serious complications than fundoplication and rarely requires general anaesthetic.’

The Society of American Gastrointestinal and Endoscopic Surgeons published a review on endoluminal treatment of GORD in February 2013[10]. The review made the following recommendation for endoscopic radiofrequency ablation:

‘Stretta is considered appropriate therapy for patients being treated for GERD who are 18 years of age or older, who have had symptoms of heartburn, regurgitation, or both for 6 months or more, who have been partially or completely responsive to anti-secretory pharmacologic therapy, and who have declined laparoscopic fundoplication.

Quality of Evidence: (++++). GRADE Recommendation: Strong'

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Laparoscopic insertion of a magnetic bead band for gastro-oesophageal reflux disease. NICE interventional procedures guidance 431 (2012).
- Endoluminal gastroplication for gastro-oesophageal reflux disease. NICE interventional procedures guidance 404 (2011).
- Endoscopic augmentation of the lower oesophageal sphincter using hydrogel implants for the treatment of gastro-oesophageal reflux disease. NICE interventional procedures guidance 222 (2007).
- Endoscopic injection of bulking agents for gastro-oesophageal reflux disease. NICE interventional procedures guidance 55 (2004).

Clinical guidelines

- Dyspepsia: management of dyspepsia in adults in primary care. NICE clinical guideline 17 (2004, last modified 2005).

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Professor S Attwood, Professor H Barr (Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland); Dr M Thomson (British Society of Gastroenterology).

- None of the specialist advisers has performed the procedure.
- All 3 specialist advisers consider the procedure to be definitely novel and of uncertain safety and efficacy.
- Laparoscopic Nissen's fundoplication and endoscopic fundoplication such as transoral incision-less fundoplication would be the comparators to this procedure.
- One specialist adviser notes that there is discussion as to whether this procedure denervates the oesophagus making it less sensitive to refluxate.

- Adverse events reported in the literature include delayed gastric emptying, oesophageal perforation and death.
- One specialist adviser noted a theoretical increased risk of adenocarcinoma of the oesophagus in the long term.
- The key efficacy outcomes include long-term objective evidence (pH studies), long-term symptomatic control, quality of life and decrease or cessation of PPI use.
- One specialist adviser noted that the procedure may provide short-term benefit and it may make the oesophagus less sensitive to refluxate but damage and degeneration may continue. It must not alter the genetics of the mucosal lining.
- One specialist adviser noted that there is no randomised clinical trial of its use compared with Nissen fundoplication (which it is claimed to be safer than, but it is clearly not as effective) and no comparison with other less invasive reflux therapies such as Stapled Endoplication, or Esophyx, or Linx magnetic beads, or the Endostim device.
- Advanced endoscopic skills are needed to undertake the procedure safely. One specialist adviser considered the potential impact of this procedure on the NHS to be major, in terms of patients eligible for treatment and use of resources; 1 described the potential impact as moderate and 1 described the potential impact as minor.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme was unable to gather patient commentary for this procedure.

Issues for consideration by IPAC

None other than those described above.

References

1. Perry KA, Banerjee A, Melvin WS (2012) Radiofrequency energy delivery to the lower esophageal sphincter reduces esophageal acid exposure and improves GERD symptoms: a systematic review and meta-analysis. Surgical Laparoscopy, Endoscopy & Percutaneous Techniques 22: 283–8

2. Arts J, Bisschops R, Blondeau K et al. (2012) A double-blind sham-controlled study of the effect of radiofrequency energy on symptoms and distensibility of the gastro-esophageal junction in GERD. American Journal of Gastroenterology 107: 222–30

3. Coron, E, Sebille V, Cadiot G et al. (2008) Clinical trial: Radiofrequency energy delivery in proton pump inhibitor-dependent gastro-oesophageal reflux disease patients. Alimentary Pharmacology & Therapeutics 28: 1147–58

4. Jeansonne LO, White BC, Nguyen V et al. (2009) Endoluminal full-thickness plication and radiofrequency treatments for GERD. Archives of Surgery 144: 19–24

5. Dughera L, Navino M, Cassolino P et al. (2011) Long-Term Results of Radiofrequency Energy Delivery for the Treatment of GERD: Results of a Prospective 48-Month Study. Diagnostic & Therapeutic Endoscopy 507157

6. Gao X, Wang Z, Wu J et al. (2011) Radiofrequency treatment on respiratory symptoms due to gastroesophageal reflux disease. Chinese Medical Journal 124: 1006–9

7. Liu H-F, Zhang J-G, Li J et al. (2011) Improvement of clinical parameters in patients with gastroesophageal reflux disease after radiofrequency energy delivery. World Journal of Gastroenterology 17: 4429–33

8. Madan AK, Ternovits CA, and Tichansky DS (2006) Emerging endoluminal therapies for gastroesophageal reflux disease: adverse events. American Journal of Surgery 192: 72–5

9. McLoughlin P, Jamieson G, Maddern G (2006) Endoscopic treatments for gastro-oesophageal reflux disease (GORD): an Accelerated Systematic Review. ASERNIP-S Review No 54. Adelaide, South Australia

10. Auyang ED, Carter P, Rauth T et al. (2012) Clinical Spotlight Review – Endoluminal Treatments for Gastroesophageal Reflux Disease (GERD). Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)

Appendix A: Additional papers on endoscopic radiofrequency ablation for gastro-oesophageal reflux disease

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Arts J, Sifrim D, Rutgeerts P. (2007) Influence of radiofrequency energy delivery at the gastroesophageal junction (the Stretta procedure) on symptoms, acid exposure, and esophageal sensitivity to acid perfusion in gastroesophagal reflux disease. Digestive Diseases & Sciences 52: 2170-2177	Case series n=13 FU=6 months	The procedure induces subjective improvement in GORD symptoms and decreased acid exposure.	Larger studies are included in table 2.
Aziz AM, El-Khayat HR, Sadek A et al. (2010) A prospective randomized trial of sham, single-dose Stretta, and double-dose Stretta for the treatment of gastroesophageal reflux disease. Surgical Endoscopy 24 (4) 818-825	RCT n=36 FU=12 months	RF ablation significantly reduced GORD HRQL, use of PPI drugs, oesophageal acid exposure, lower oesophageal sphincter pressure and grade of oesophagitis compared with a sham procedure.	Study is included in Perry et al, 2012 systematic review and meta-analysis.
Chen D, Barber C, McLoughlin P et al. (2009) Systematic review of endoscopic treatments for gastro-oesophageal reflux disease. British Journal of Surgery 96: 128–36	Systematic review 33 studies on 7 different procedures	At present there is insufficient evidence to determine the safety and efficacy of endoscopic procedures for gastro-oesophageal reflux disease, particularly in the long term.	A more recent systematic review is included in table 2.
Cipolletta L, Rotondano G, Dughera L. (2005) Delivery of radiofrequency energy to the gastroesophageal junction (Stretta procedure) for the treatment of gastroesophageal reflux disease. Surgical Endoscopy 19:849-853	Case series n=32 FU= 12 months	RF delivery to the lower oesophageal sphincter is safe and significantly improves symptoms and quality of life in selected GORD patients.	Study is included in Perry et al, 2012 systematic review and meta-analysis.
Corley DA, Katz P, Wo JM et al. (2003) Improvement of gastroesophageal reflux symptoms after radiofrequency energy: a randomized, sham-controlled trial. Gastroenterology 125:668-676	RCT n=64 FU=6 months	Heartburn score at 6 months: • RFA=-1.6 • Sham=0.6, p=0.01	Study is included in Perry et al, 2012 systematic review and meta-analysis.
DiBiase JK, Brand RE, Quigley EM. (2002) Endoluminal delivery of radiofrequency energy to the gastroesophageal junction in uncomplicated GERD: efficacy and potential mechanism of action.American Journal of Gastroenterology 97:833-842	Case series n=18 FU= 6 months	RF energy delivery to the gastrooesophageal junction provides effective symptomatic relief in the short term in patients with uncomplicated GORD.	Study is included in Perry et al, 2012 systematic review and meta-analysis.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Dundon JM, Davis SS, Hazey JW et al. (2008) Radiofrequency energy delivery to the lower esophageal sphincter (Stretta procedure) does not provide long-term symptom control. Surgical Innovation 15:97-301.	Case series n=32 FU=53 months	RF ablation was effective in reducing symptoms in 40% of patients. 59% (19/32) of patients needed antireflux surgery about 6 months after RF ablation.	Study is included in Perry et al, 2012 systematic review and meta-analysis.
Fry LC, Monkemuller K, Malfertheiner P. (2007) Systematic review: endoluminal therapy for gastro-oesophageal reflux disease: evidence from clinical trials. European Journal of Gastroenterology & Hepatology 19: 1125-1139	Systematic review n=15 studies n=1298 patients FU= 3 to 48 months	Currently there are not enough scientific and clinical data on safety, efficacy, and durability to support the routing use of endoluminal therapies in GORD.	Systematic review without meta analysis of the same studies / patients identified in this overview.
Go MR, Dundon JM, Karlowicz DJ et al. (2004) Delivery of radiofrequency energy to the lower esophageal sphincter improves symptoms of gastroesophageal reflux. Surgery 136: 786-794	Case series n=50 FU= 10 months	Stretta improves heartburn symptoms overall and in patients with poor outcome after anti-reflux surgery, with low procedural risk.	Study is included in Perry et al, 2012 systematic review and meta-analysis.
Higuchi K, Fujiwara Y, Okazaki H et al. (2007) Feasibility, safety, and efficacy of the Stretta procedure in Japanese patients with gastroesophageal reflux disease: first report from Asia. Journal of Gastroenterology 42:205-210.	Case series n=9 FU= 6 months	The Stretta procedure safely reduced GORD symptoms and medication use.	Study is included in Perry et al, 2012 systematic review and meta-analysis.
Houston H, Khaitan L, Holzman M et al. (2003) First year experience of patients undergoing the Stretta procedure. Surgical Endoscopy 17: 401–4	Case series n=41 FU=6 months	The Stretta procedure is a promising new endoscopic treatment for GERD. It significantly improves GERD symptoms and quality of life while eliminating the need for proton pump inhibitors in the majority of patients	Study is included in Perry et al, 2012 systematic review and meta-analysis.
Islam S, Geiger JD, Coran A et al. (2004) Use of radiofrequency ablation of the lower esophageal sphincter to treat recurrent gastroesophageal reflux disease. Journal of Pediatric Surgery 39:282-286	Case series n=6 FU= Not reported	RF treatment for the lower oesophageal sphincter is a potentially successful modality to treat GORD in children, Long-term follow-up is required.	Larger studies are included in table 2.
Lutfi RE, Torquati A, Kaiser J et al. (2005) Three years' experience with the Stretta procedure: did it really make a difference? Surgical Endoscopy 19:289-295	Case series n=61 FU=26 months	43% (26/61) of patients were off PPIs after the procedure. 73% (45/61) of patients were satisfied with the procedure.	Study is included in Perry et al, 2012 systematic review and meta-analysis.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Mattar SG, Qureshi F, Taylor D et al. (2006) Treatment of refractory gastroesophageal reflux disease with radiofrequency energy (Stretta) in patients after Roux-en-Y gastric bypass. Surgical Endoscopy 20:850-854	Case series n=7 FU= 20 months	Stretta is a valid option in the treatment of persistent GORD for patients that have undergone gastric bypass.	Study is included in Perry et al, 2012 systematic review and meta-analysis.
Mavrelis P, Abdel Aziz AM, Rearick C et al. (2007) Longer term clinical outcomes after radiofrequency therapy for refractory gastroesophageal reflux disease (GERD). Practical Gastroenterology 31:73-80.	Case series n=32 FU= 2.5 years	In patients with refractory GORD symptoms the Stretta procedure was feasible, safe, and partially effective in decreasing symptoms and proton pump inhibitor use.	Larger studies are included in table 2.
McClusky III DA, Khaitan L, Swafford VA et al. (2007) Radiofrequency energy delivery to the lower esophageal sphincter (Stretta procedure) in patients with recurrent reflux after antireflux surgery: Can surgery be avoided? Surgical Endoscopy 21:1207-1211	Case series n=8 FU= 12 months	Based on this small series, the Stretta procedure significantly reduces subjective symptoms of GORD	Larger studies are included in table 2. This study represents a subgroup of patients who have previously undergone anti-reflux surgery
Meier PN, Nietzschmann T, Akin I et al. (2007) Improvement of objective GERD parameters after radiofrequency energy delivery: a European study. Scandinavian Journal of Gastroenterology 42:911-916	Case series n=60 FU= 12 months	RF ablation is well tolerated and effective in the treatment of GORD. It has a favourable impact on medication requirements, lower oesophageal sphincter pressure, acid exposure, and GORD symptoms	Study is included in Perry et al, 2012 systematic review and meta-analysis.
Noar MD and Lotfi-Emran S. (2007) Sustained improvement in symptoms of GERD and antisecretory drug use: 4-year follow-up of the Stretta procedure.[see comment]. Gastrointestinal Endoscopy 65:367-372	Case series n=109 FU=4 years	At baseline, 100% of patients were on proton pump inhibitor medication. At 4-year follow-up, 75% were on no medication or were using over-the-counter drug antacids only. A total of 85% of patients had reduced proton pump inhibitor use by half or had eliminated it completely. Significant decrease in heartburn score.	Study is included in Perry et al, 2012 systematic review and meta-analysis.
Noar MD, Noar E (2008) Gastroparesis associated with gastroesophageal reflux disease and corresponding reflux symptoms may be corrected by radiofrequency ablation of the cardia and esophagogastric junction. Surgical Endoscopy 22: 2440– 4	Case series n=31 FU=1 year	RF ablation has been demonstrated to correct gastroparesis. Patients' symptoms improved significantly.	Larger studies are included.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Reymunde A and Santiago N. (2007) Long-term results of radiofrequency energy delivery for the treatment of GERD: sustained improvements in symptoms, quality of life, and drug use at 4-year follow-up. Gastrointestinal Endoscopy 65:361-366	Case series n=83 FU=4 years	At baseline, 100% of patients were on proton pump inhibitor medication. This reduced significantly to 13.7% of patients at 4-year follow-up ($p < 0.001$) Mean GORD symptom score improved from 2.7 points at baseline to 0.6 points at 4-year follow-up ($p < 0.001$).	Study is included in Perry et al, 2012 systematic review and meta-analysis.
Richards WO, Scholz S, Khaitan L et al. (2001) Initial experience with the Stretta procedure for the treatment of gastroesophageal reflux disease. Journal of Laparoendoscopic and Advanced Surgical Techniques Part A 11: 267–73	Case series n=25 FU=3months	2 complications: 1 ulcerative oesophagitis and gastroparesis 10 days after the procedure, 1 pancreatitis on postoperative day 27 (probably unrelated to RF ablation). 62% (8/13) patients were off all antisecretory medication at 3 months.	Larger studies with longer follow-up are included.
Richards WO, Houston HL, Torquati A et al. (2003) Paradigm shift in the management of gastroesophageal reflux disease. Annals of Surgery 237: 638-647	Non-randomised comparative study n=140 FU=7 months	Patients undergoing Stretta are highly satisfied and have improved GERD symptoms and quality of life comparable to laparoscopic fundoplication. The Stretta procedure is an effective alternative to LF in well-selected patients	Study is included in Perry et al, 2012 systematic review and meta-analysis.
Tam WC, Schoeman MN, Zhang Q et al. (2003) Delivery of radiofrequency energy to the lower oesophageal sphincter and gastric cardia inhibits transient lower oesophageal sphincter relaxations and gastro-oesophageal reflux in patients with reflux disease. Gut 52:479-485	Case series n=20 FU= 1 year	RF ablation has significant effects on lower oesophageal sphincter function associated with improvement in the anti-reflux barrier	Study is included in Perry et al, 2012 systematic review and meta-analysis.
Torquati A, Houston HL, Kaiser J et al. (2004) Long-term follow-up study of the Stretta procedure for the treatment of gastroesophageal reflux disease. Surgical Endoscopy 18: 1475-1479	Case series n=36 FU=27 months	The Stretta procedure results in a statistical significant long-term decrease in GERD symptoms and PPI use. The treatment effect is durable beyond 2 years, and 56% of patients had discontinued their user of all antisecretory drugs	Study is included in Perry et al, 2012 systematic review and meta-analysis.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Triadafilopoulos G, DiBaise JK, Nostrant TT et al. (2002) The Stretta procedure for the treatment of GERD: 6 and 12 month follow-up of the U.S. open label trial.[see comment]. Gastrointestinal Endoscopy 55:149-156	Case series n=118 FU=12 months	At 12-months follow-up, 68% of patients had at least a 50% reduction (improvement) in heartburn scores, 65% had at least a 50% reduction (improvement) in HRQoL scores, and 99% had at least a 50% improvement in satisfaction score. At baseline, 88.1% of patients required daily proton pump inhibitors; after RF ablation only 30% required this medication ($p < 0.0001$).	Study is included in Perry et al, 2012 systematic review and meta-analysis.
Triadafilopoulos G (2004) Changes in GERD symptom scores correlate with improvement in esophageal acid exposure after the Stretta procedure. Surgical Endoscopy 18: 1038-1044	Case series n=118 FU=6 months	Responders had significant improvement in oesophageal acid exposure, whereas nonresponders had less or no change.	Post-hoc analysis of date presented in an earlier paper by the same author.
White B, Jeansonne LO, Cook M et al. (2009) Use of endoluminal antireflux therapies for obese patients with GERD. Obesity Surgery 19: 783–7	Non-randomised comparative study n=22 FU=1.5 years	There were no treatment associated complications. Overall failure rate=28% (10% Plicator, 42% Stretta, p=0.11)	Larger studies are included.
Wolfsen HC and Richards WO. (2002) The Stretta procedure for the treatment of GERD: a registry of 558 patients. Journal of Laparoendoscopic & Advanced Surgical Techniques A 12:395-402	Case series n=558 FU=8 months	At baseline, 93.6% of patients required daily proton pump inhibitor therapy. Following the RF procedure, 51.0% of patients required no antisecretory medication.	Study is included in Perry et al, 2012 systematic review and meta-analysis.

Appendix B: Related NICE guidance for endoscopic radiofrequency ablation for gastro-oesophageal reflux disease

Guidance	Recommendations
Interventional procedures	**Laparoscopic insertion of a magnetic bead band for gastro-oesophageal reflux disease. NICE interventional procedures guidance 431 (2012)** 1.1 The evidence on the safety and efficacy of laparoscopic insertion of a magnetic bead band for gastro-oesophageal reflux disease (GORD) is limited in quantity. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research. 1.2 Clinicians wishing to undertake laparoscopic insertion of a magnetic bead band for GORD should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, the use of NICE's information for the public is recommended. • Audit and review clinical outcomes of all patients having laparoscopic insertion of a magnetic bead band for GORD (see section 3.1). 1.3 NICE encourages further research and collaborative data collection on laparoscopic insertion of a magnetic bead band for GORD. Clear descriptions of patient selection are particularly important. Perioperative and long-term complications should be reported, together with details of long-term efficacy, including the need for further procedures and medication to control symptoms of GORD. NICE may review the procedure on publication of further evidence. **Endoluminal gastroplication for gastro-oesophageal reflux disease. NICE interventional procedures guidance 404 (2011).** 1.1 The evidence on endoluminal gastroplication for gastro-oesophageal reflux disease (GORD) raises no major safety

	concerns. Evidence from a number of randomised controlled trials (RCTs) shows a degree of efficacy in terms of reduced medication requirement in the short term, but changes in other efficacy outcomes are inconsistent and there is no good evidence of sustained improvement in oesophageal pH measurements. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research. 1.2 Clinicians wishing to undertake endoluminal gastroplication for GORD should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients and their carers understand the uncertainty about the procedure's efficacy, particularly in the long term, and provide them with clear written information. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended (available from www.nice.org.uk/guidance/IPG404/publicinfo). • Audit and review clinical outcomes of all patients having endoluminal gastroplication for GORD (see section 3.1). 1.3 Any further studies should include measurements of oesophageal pH and report long-term outcomes. **Endoscopic augmentation of the lower oesophageal sphincter using hydrogel implants for the treatment of gastro-oesophageal reflux disease. NICE interventional procedures guidance 222 (2007).** 1.1 There is limited evidence of short-term efficacy on endoscopic augmentation of the lower oesophageal sphincter using hydrogel implants for the treatment of gastro-oesophageal reflux disease (GORD). This evidence also raises concerns about the procedure's safety. Therefore, this procedure should not be used without special arrangements for consent and for audit. 1.2 Clinicians wishing to undertake endoscopic augmentation of the lower oesophageal sphincter using hydrogel implants for the treatment of GORD should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, use of the Institute's information for patients ('Understanding NICE guidance') is

	recommended. • Audit and review clinical outcomes of all patients having endoscopic augmentation of the lower oesophageal sphincter using hydrogel implants for the treatment of GORD (see section 3.1). 1.3 Any adverse events resulting from the procedure should be reported to the Medicines and Healthcare products Regulatory Agency (MHRA). **Endoscopic injection of bulking agents for gastro-oesophageal reflux disease. NICE interventional procedures guidance 55 (2004).** 1.1 Current evidence on the safety and efficacy of endoscopic injection of bulking agents for gastro-oesophageal reflux disease does not appear adequate for this procedure to be used without special arrangements for consent and for audit or research. 1.2 Clinicians wishing to undertake endoscopic injection of bulking agents for gastro-oesophageal reflux disease should take the following action. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. Use of the Institute's information for the public is recommended. • Audit and review clinical outcomes of all patients having endoscopic injection of bulking agents for gastro-oesophageal reflux disease. 1.3 Publication of safety and efficacy outcomes will be useful in reducing the current uncertainty. The Institute may review the procedure upon publication of further evidence.

Clinical guidelines	**Dyspepsia: management of dyspepsia in adults in primary care. NICE clinical guideline 17 (2004, last modified 2005)** 1.6.1 Gastro-oesophageal reflux disease (GORD) refers to endoscopically determined oesophagitis or endoscopy-negative reflux disease. Patients with uninvestigated 'reflux-like' symptoms should be managed as patients with uninvestigated dyspepsia. 1.6.2 Offer patients with GORD a full-dose PPI for 1 or 2 months. • *PPIs are more effective than H2RAs at healing oesophagitis in trials. Healing occurred in 22% of patients on placebo, 39% of patients on H2RAs (a number needed to treat of six) and 76% of patients on PPIs (a number needed to treat of two). There is considerable variation in the findings of trials.* • *In trials, extending treatment to 2 months increased healing of oesophagitis by a further 14%.* • *If patients have severe oesophagitis and remain symptomatic, double-dose PPI for a further month may increase the healing rate.* • *Limited evidence shows that antacids are no more effective at healing oesophagitis than placebo.* • *On balance, PPIs appear more effective than H2RAs in endoscopy-negative reflux disease. In head-to-head trials 53% of patients became symptom-free on PPI compared with 42% receiving H2RAs, although the difference was not statistically significant. The same pattern of benefit is apparent in placebo-controlled trials.* 1.6.3 If symptoms recur following initial treatment, offer a PPI at the lowest dose possible to control symptoms, with a limited number of repeat prescriptions. • *The majority of patients will experience a recurrence of symptoms within 1 year.* • *PPIs are more effective than H2RAs at maintaining against relapse of oesophagitis in trials of 6–12 months duration. Relapse occurred in 59% of patients on H2RA and 20% of patients on PPI (a number needed to treat of three). There is considerable variation in the findings of trials.*

- *PPIs at full dose are more effective than PPIs at low dose in trials of 6–12 months duration. Relapse of oesophagitis occurred in 28% of patients on low-dose PPI and 15% of patients on full-dose PPI (a number needed to treat of eight). There is considerable variation in the findings of trials.*

- *There are no long-term trials in endoscopy-negative reflux disease. However, the most cost-effective approach appears to be to offer patients intermittent 1-month full-dose or as-required PPI therapy, rather than continuous therapy.*

1.6.4 Discuss using the treatment on an as-required basis with patients to manage their own symptoms.

- *Patients with endoscopy-negative reflux disease and using PPI therapy as required (waiting for symptoms to develop before taking treatment) reported similar 'willingness to continue' to those on continuous PPI therapy.*

- *Patients taking therapy as required used about 0.4 tablets per day, averaged across studies of 6–12 months duration. Taking therapy when symptoms occur may help patients to tailor their treatment to their needs.*

1.6.5 Offer H_2RA or prokinetic therapy* if there is an inadequate response to a PPI.

- *PPIs are more effective than H2RAs or prokinetics at reducing dyspeptic symptoms in trials of patients with GORD. However, individual patients may respond to H2RA or prokinetic therapy.*

1.6.6 Surgery cannot be recommended for the routine management of persistent GORD although individual patients whose quality of life remains significantly impaired may value this form of treatment.

- *Open surgery is no better than long-term medical therapy at achieving remission from symptoms.*

- *Laparoscopic surgery is no better than open surgery at achieving remission from symptoms.*

- *There is a small (0.1−0.5%) but important post-operative mortality associated with anti-reflux surgery.*

	1.6.7 Patients who have had dilatation of an oesophageal stricture should remain on long-term full-dose PPI therapy. • *In one large randomised controlled trial (RCT) of patients who have had oesophageal stricture, 30% of the PPI group required repeat dilatation compared with 46% of the ranitidine group.* * Cisapride is no longer licensed in the UK and evidence is sparse for domperidone or metoclopramide.

Appendix C: Literature search for endoscopic radiofrequency ablation for gastro-oesophageal reflux disease

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	18/04/2013	Issue 3 of 12, Mar 2013
Database of Abstracts of Reviews of Effects – DARE (CRD website)	18/04/2013	Issue 1 of 4, Jan 2013
HTA database (CRD website)	18/04/2013	Issue 1 of 4, Jan 2013
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	18/04/2013	Issue 3 of 12, Mar 2013
MEDLINE (Ovid)	18/04/2013	1946 to April Week 2 2013
MEDLINE In-Process (Ovid)	18/04/2013	April 17, 2013
EMBASE (Ovid)	18/04/2013	1974 to 2013 Week 15
CINAHL (NLH Search 2.0 or EBSCOhost)	18/04/2013	1981 to present
JournalTOCS	18/04/2013	n/a

Trial sources searched

- Current Controlled Trials *meta*Register of Controlled Trials – *m*RCT
- Clinicaltrials.gov
- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database

Websites searched

- National Institute for Health and Clinical Excellence (NICE)
- Food and Drug Administration (FDA) - MAUDE database
- French Health Authority (FHA)
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- Conference search
- Evidence Updates (NHS Evidence)
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	exp Gastroesophageal Reflux/
2	exp Esophagitis, Peptic/

3	((gastro-esophag* or gastroesophag* or gastro-oesophag* or oesophag* or esophag* or gastric* or acid*) adj3 reflux*).tw.
4	Esophageal Motility Disorders/
5	((Esophag* or Oesophag*) adj3 (Peptic* or dysmot* or motilit* or function*) adj3 (disorder* or impair* or defect*)).tw.
6	Heartburn/
7	heartburn*.tw.
8	Dyspepsia/
9	dyspep*.tw.
10	Barrett Esophagus/
11	(Barrett* adj3 (esophag* or oesophag*)).tw.
12	GORD.tw.
13	GERD.tw.
14	indigestio*.tw.
15	regurg*.tw.
16	or/1-15
17	Catheter Ablation/
18	((cathet* or electric*) adj3 ablat*).tw.
19	((Radiofreq* or radio-freq* or radio freq*) adj3 (ablat* or energ*)).tw.
20	RFA.tw.
21	RF.tw.
22	(Therm* adj3 lesion*).tw.
23	Cicatrix/
24	(scar* or cicatri*).tw.
25	Stretta*.tw.
26	exp Balloon Dilation/
27	((Balloon* or Flexib*) adj3 (dilat* or cathet*)).tw.
28	or/17-27

29	16 and 28
30	Animals/ not Humans/
31	29 not 30
32	limit 31 to ed=20120229-20121205