Clinical trial: radiofrequency energy delivery in proton pump inhibitor-dependent gastro-oesophageal reflux disease patients

E. CORON*, V. SEBILLE†, G. CADIOT‡, F. ZERBIB§, P. DUCROT††, P. DUCROT∗∗, P. POUDEROUX+++ , J. ARTS†††, M. LE RHUN*, T. PICHE§§, S. BRULEY DES VARANNESS*,∗∗∗ & J. P. GALMICHE∗,∗∗∗
CONSORTIUM DE RECHERCHE INDÉPENDANT SUR LE TRAITEMENT ET L’EXPLORATION DU REFLUX GASTRO-ÖSEPHAGIEN ET DE L’ENDOBRAHYÖSEPHAGE (CRITERE)

SUMMARY
Background
Radiofrequency (RF) energy delivery is an endoscopic procedure developed for the treatment of gastro-oesophageal reflux disease.

Aim
To compare RF and a proton pump inhibitor strategy (PPI) in PPI-dependent patients by carrying out a prospective, randomized trial.

Methods
Patients with PPI-dependent typical reflux symptoms were randomly allocated to either RF or PPI regimen alone. The primary endpoint, evaluated at 6-month, was defined as the possibility for the patient to stop or to decrease PPI use to <50% of the effective dose required at baseline.

Results
In the RF group, 18/20 patients stopped (n = 3) or decreased (n = 15) PPI use as compared to eight of 16 in the PPI group (P = 0.01). None of the control patients could stop PPI. Health-related quality of life scores were not different between groups. No significant change in oesophageal acid exposure (OAE) was noted between baseline and 6-months after RF. No severe complication was reported.

Conclusions
Radiofrequency energy delivery is a safe and effective therapeutic option, allowing reduction in or discontinuation of PPI therapy in patients with PPI-dependent symptoms, without loss of quality of life. However, in a majority of patients, PPI therapy cannot be completely stopped. The efficacy of RF does not seem to be related to a decrease in OAE.
INTRODUCTION

Gastro-oesophageal reflux disease (GERD) is a common chronic condition that affects up to 20% of adults weekly.\(^1\) Frequent symptoms may severely affect health-related quality of life (HR-QOL).\(^2\) Proton pump inhibitors (PPIs) represent the mainstay of therapy of a vast majority of GERD patients as they are the most potent drugs for both the cure of lesions of oesophagitis and the control of symptoms.\(^3\) However, in a substantial group of patients, symptoms and/or oesophagitis can recur shortly after the end of treatment. In these patients, the key issue is the long-term control of the disease, which can be achieved by different means including maintenance drug therapy, anti-reflux surgery and, potentially, endoscopic procedures.

Maintenance treatment with PPIs is highly effective, but has some limitations: (i) PPIs do not interfere with the underlying cause of reflux; (ii) PPIs represent one of the highest drug expenses in many countries; (iii) the efficacy of PPIs upon GERD symptoms and HR-QOL is not optimal as up to 58% of patients are not fully satisfied with their PPI therapy;\(^4\) and (iv) patients’ compliance toward PPI therapy is probably more limited than initially thought. For instance, it has been reported recently that most patients on long-term maintenance therapy took their medication intermittently.\(^5\) This may reflect the fact that an important proportion of patients, especially the youngest patients, are concerned with safety issues and risks of a life-long drug therapy.\(^6\)–\(^9\)

Antireflux surgery (ARS) is an alternative to long-term maintenance therapy. However, there is no evidence of superiority of ARS over long-term PPI treatment when patients are allowed to adjust the PPI dose according to their individual needs in GERD.\(^10\) Moreover, many patients continue to use regular anti-reflux medications after surgery.\(^11\) Finally, it is not devoid of morbidity and even carries the risk of a small but not negligible mortality risk.\(^12\)

As both medical and surgical therapies have limitations, a variety of endoscopic techniques have been developed in the past few years.\(^13\) Most of these techniques have been withdrawn for lack of efficacy or for safety reasons. The Stretta procedure is an endoluminal radiofrequency (RF) energy delivery technique, which has been shown to be effective for the treatment of GERD in various open-label trials\(^14\)–\(^22\) and in one sham-controlled trial.\(^23\) The latest study reported that GERD symptoms and HR-QOL improvement were significantly better at 6 months in the active RF-treated group than in the sham-treated group. However, no difference could be noted in the percentage of patients using daily PPIs between both groups 6 months after the procedure and the mechanisms of RF effect are not completely clear, especially with respect to the ability of the technique to reduce or not oesophageal acid exposure (OAE). Moreover, none of the above trials focused on PPI use as a primary endpoint in truly drug-dependent GERD patients.

We therefore conducted a prospective, randomized, controlled trial to compare RF and a PPI strategy in truly PPI-dependent GERD patients.

METHODS

Study design

Inclusion/exclusion criteria. From January 2003 to March 2006, patients referred to two secondary and six tertiary referral centres (Le Havre, Nîmes, Nantes, Reims, Bordeaux, Rouen, Nice and Bruges) for chronic GERD symptoms were considered for enrolment into the study. The inclusion criteria were as follows: (1) age 18 years or older, (2) diagnosis of GERD established by either (i) 24-h oesophageal pH monitoring (performed off medications) showing an abnormal OAE (pH < 4 at least 4% of time) and/or (ii) an upper gastrointestinal (GI) endoscopy showing oesophagitis grade A or B in Los Angeles (LA) classification, (3) presence of typical symptoms of GERD (heartburn and/or regurgitation with at least three episodes of typical symptoms per week in the absence of PPI therapy), (4) adequate symptom relief obtained with PPIs, but needing maintenance with at least standard dose (see below).

Conversely, patients with one or more of the following criteria were excluded: (i) presence of Barrett’s oesophagus >3 cm and/or with dysplasia and/or previously treated; (ii) presence of hiatus hernia >3 cm; (iii) presence of oesophagitis grade C or D in LA classification; (iv) presence of oesophageal stricture or acha- lasia; (v) history of oesophageal or gastric surgery; (vi) presence of gastric or oesophageal varices; (vii) presence of a cardiac pacemaker or any other implanted electro-medical device; (viii) impossibility to stop an anticoagulant therapy or severe coagulopathy; (ix) any contraindication to general anaesthesia; (x) life threatening disorders with a life expectancy of <1 year;
(xi) high alcohol consumption (>60 g/day); (xii) morbid obesity (BMI over 35); (xiii) patients whose symptoms are adequately relieved with half-dose PPI regimen or intermittent acid suppression; and (xiv) inability to understand the study protocol or refusal to give informed consent.

**Run-in phase (Figure 1a).** During a 6-to-12 week run-in phase, PPI dependent patients underwent a prerandomization work-up (Figure 1) to determine frequency and intensity of typical GERD symptoms, HR-QOL and PPI needs and to perform 24-h oesophageal pH monitoring, oesophageal manometry and upper GI endoscopy at baseline (if these examinations had not been performed within the previous 6 months).

In particular, baseline PPI needs were determined carefully according to a standardized protocol. Patients were asked to take their PPIs daily and the effective dose (ED) was defined as the dose allowing adequate control of symptoms during 3 weeks. Adequate control was defined as <3 symptomatic episodes of GERD occurring per week with intensity ≤3 on a five-point Likert scale (see below). After this, patients were instructed to try decreasing this dose by half (1/2 ED) for another 3 weeks to ensure that symptoms reappeared and that control actually required the initially determined ED. Patients who were completely relieved by half-doses of PPIs (e.g. omeprazole or rabeprazole 10 mg/day) were excluded from the study.

**Randomization and follow-up (Figure 1b).** Proton pump inhibitor-dependent patients with a stable established ED were randomized either to maintenance PPI regimen alone (control group) or to RF (Stretta procedure). Treatment status was assigned by using a centrally generated, stratified (by study site) block randomization. Each block consisted of four treatments.

---

**Figure 1.** Trial design. (a) Before randomization: assessment and determination of the minimal effective proton pump inhibitor (PPI) dose (ED = effective dose required for adequate symptom relief). (b) After randomization to PPI regimen alone (control group) or radiofrequency therapy (RF), two attempts were carried out to reduce or stop PPI according to a standard protocol (see text). The primary outcome (ability and willingness of the patient to stop PPI or to reduce PPI use by at least 50%) was determined between weeks 24 and 30.
(i.e. two RF and two PPI). If eligibility criteria were met, the principal investigator in each centre was allowed to open the appropriate sealed envelope.

The effective PPI dose (ED) was maintained for 6 weeks following randomization to the control or RF group. After this, the first attempt to decrease PPI use and eventually to stop PPI was performed by the patient himself/herself according to previously explained recommendations to maintain symptom control. In the case of symptom relapse, patients were instructed to return to their previous ED regimen for another 6 weeks before the second step-down attempt.

Outcome measures (Figure 1b). The primary endpoint, evaluated as a dichotomous variable at the 6 month visit, was the possibility or not for the patient to stop or to decrease PPI use to <50% ED during the last 6 weeks. Secondary end-points included quality of life (QOL) (generic SF-36, specific REFLUX-QUAL HR-QOL), acid exposure and endoscopic assessments at 6 months and clinical follow-up at 1 year.

Radiofrequency procedure

The RF procedure was performed according to a previously described technique under general anaesthesia. Briefly, the Stretta system (Curon Medical, Sunnyvale, CA, USA) used a RF generator and a flexible catheter with balloon-basket assembly with four electrode needles that penetrate into the submucosa and muscular layers to deliver RF energy. This was repeated along various lengths in the lower oesophagus and gastric cardia to deliver RF energy to 56 sites. After completion of the procedure and catheter removal, the diagnostic endoscopy procedure was repeated to verify the absence of complications such as bleeding or perforation.

Assessments

Symptom scores. All patients were invited to fill a standardized questionnaire that included questions about the intensity of typical reflux symptoms (i.e. heartburn, regurgitation and epigastric burning). The intensity of typical symptoms was assessed using the following five-point Likert scale: 1 = no symptom, 2 = mild symptom that can be ignored by the patient, 3 = mild symptom that cannot be ignored by the patient, 4 = symptom negatively affecting concentration, 5 = intense symptoms severely affecting daily life activities or sleep.

HR-QOL assessment. Gastro-oesophageal reflux disease HR-QOL and general HR-QOL were assessed using the REFLUX-QUAL questionnaire and the medical outcomes 36-item Short-Form Health Survey (SF-36). The SF-36 is an extensively-used, self-administered, generic questionnaire containing 36 items clustered into eight dimensions. Item scores for each dimension are transformed into a scale from 0 (the worst possible health state measured by the questionnaire) to 100 (the best possible health state). The REFLUX-QUAL is a French validated questionnaire consisting of 37 items divided into seven dimensions (daily life, social life, well being, mental health, fears, sleeping and feeding). Every item is graded according to a five-grade Likert scale, consisting of five possible answers, each scored from 1 (‘very much’ or ‘permanently’) to 5 (‘never’ or ‘not at all’). These scores are linearly transformed from 1, 2, 3, 4, 5 to 0, 25, 50, 75, 100 respectively (0 representing the worst HR-QOL and 100 the best HR-QOL). The global REFLUX-QUAL score is determined as the mean of the scores of the seven dimensions and is also graded from 0 to 100. According to previous results, we considered HR-QOL as good or excellent if the REFLUX-QUAL was >80.

PPI needs. Proton pump inhibitor needs were monitored at each visit using the diary completed every day by the patient. The results were expressed in terms of ED (mg/day), mean daily consumption and ability or not to decrease daily PPI use below ED 50% or to stop PPI therapy.

Oesophageal pH monitoring, manometry and endoscopy were performed and reported according to previously described methods.

Statistical analysis

A sample size of 100 patients was initially calculated to be able to detect a difference of 30% between the control and RF groups on the primary endpoint (possibility for the patient to stop or to decrease PPI use to <50% ED during the last 6 weeks) with a two-sided test with a type 1 error of 5% and a power of 80%. The probability of PPI discontinuation or reduction of
at least 50% of baseline ED was assumed to be 40% and 70% in the control and RF groups, respectively.

One hundred patients were scheduled according to the trial design and statistical hypotheses, but the study was interrupted in 2006 because of the decision of Curon Ltd to stop the development and commercialization of the RF system.

According to the CONSORT statement,\(^{30}\) analysis was performed on an intention-to-treat (ITT) basis with all patients enrolled in the trial included in the analysis of the primary endpoint; patients excluded from the study were considered as negative results (i.e. unable to stop or decrease >50% PPI use). Finally, per-protocol analysis (PP) of the primary and secondary endpoints was carried out in the cohort of patients who completed the study according to the protocol without major violation.

The statistical analysis, prospectively defined, was performed using SAS statistical software (version 9.1; Cary, NC, USA). For continuous variables, the mean values and s.d. are reported. The number of patients in each category and the corresponding percentages are given for categorical variables. Normality was assessed using a Kolmogorov–Smirnov test and Student t-tests or Kruskal–Wallis tests were performed, as appropriate, for the comparison of continuous variables. Chi-squared tests or Fisher’s exact test were used, when appropriate, for the comparison of categorical variables.

**RESULTS**

Participants flow (Figure 2)

A total of 54 patients with typical symptoms and a confirmed diagnosis of GERD were included into the study. During the prerandomization work-up, 11 patients were excluded because of insufficient PPI needs (GERD symptom relief achieved with half-dose PPI regimen; \(n = 10\)) or unwillingness to participate \((n = 1)\). Therefore, 43 patients \((30\) men, mean age: 48 years) with PPI-dependent typical reflux symptoms were randomized to either RF \((n = 23)\) or maintenance PPI therapy alone \((n = 20)\). These 43 patients represent the cohort for ITT analysis. Patients were well-matched at baseline regarding demographic, clinical, endoscopic and 24-h pH data (Table 1). After randomization, seven patients were lost to follow-up or withdrew their consent to participate, leaving 36 patients available for PP analysis at 6 months. Between the 6th and 12th months, two patients in the control group were excluded from the study, leaving 34 patients available for the PP analysis at 12 months.

---

**Figure 2. Flow diagram of trial.**
Primary endpoint

At 6 months, ITT analysis (whereby all missing values in both groups were considered as failures to stop or decrease their PPI use to <50% ED) showed that 18/23 (78%) patients in the RF group could stop or decrease their PPI use to <50% ED vs. 8/20 (40%) in the control group (P = 0.01). PP analysis at 6 months showed similar results with 18/20 (90%) patients in the RF group being able to stop or decrease their PPI use vs. eight of 16 (50%) in the control group (P = 0.01; Table 2). Three (13%) patients in the RF group were able to stop
their PPI therapy completely vs. 0 in the control group \((P = 0.24)\); six of 20 (30%) used on-demand PPI therapy in the RF group vs. nine of 16 (56%) in the control group \((P = 0.11)\).

At 12 months, ITT analysis showed that 13/23 (56%) patients in the RF group were able to stop or decrease their PPI use vs. six of 16 (38%) in the control group \((P = 0.10)\).

Secondary endpoints

Secondary endpoints were analysed only PP since missing data could not be evaluated the same way as dichotomous variables. The intensity of regurgitation was significantly lower at 6 months in the RF group than in the control group \((P = 0.16)\). PP analysis confirmed these results with 13/20 (65%) patients in the RF group being able to stop or decrease their PPI use vs. six of 16 (38%) in the control group \((P = 0.10)\).

Global REFLUX-QUAL and SF-36 scores were not significantly different between both groups at 6 and 12 months (Table 3). However, two items of the REFLUX-QUAL, namely well-being and fears, were significantly better in the RF group compared with the PPI group at 6 months \((P = 0.05\) and \(P = 0.03)\), but this statistical difference remained at 12 months only for fears.

Monitoring of PPI needs showed that the mean daily dose of PPI was significantly lower in the RF group compared with the control group at 6 and 12 months \((12 ± 11 \text{ mg/day}; P = 0.01\) and \(16 ± 14 \text{ vs. } 37 ± 30 \text{ mg/day}; P = 0.05\) respectively) (Figure 3d).

A 24 h pH study performed at 6 months (off PPI therapy) showed that OAE was not significantly different between the RF and control groups (Figure 4). The absolute change in OAE from baseline to the 6-month assessment was not significantly different between the RF and the control group \((-2.0 ± 8.6 \text{ vs. } -1.4 ± 10.1; P = 0.472)\). In addition, upper GI endoscopy revealed that an oesophagitis was noted in 10 (four grade A and six grade B) and seven patients (five grade A, one grade B and one grade C) of the RF and the control groups, respectively \((P = 0.946)\).

No post-procedure aspiration, perforation, bleeding-requiring-transfusion or death was reported in any group. In the RF group, four patients experienced transient abdominal pain or epigastric discomfort, one episode of transient swallowing pain and two episodes of transient fever occurred. No adverse event was reported in the control group.

Table 2. Primary endpoint outcome = proton pump inhibitor (PPI) discontinuation or reduction of at least 50% of baseline effective dose in patients on PPI regimen alone (control) and after radiofrequency therapy (RF)

<table>
<thead>
<tr>
<th></th>
<th>Intention-to-treat analysis (n = 43)</th>
<th>Per-protocol analysis (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (n = 20)</td>
<td>RF (n = 23)</td>
</tr>
<tr>
<td>Stopped or decreased PPI use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 6 months* (%)</td>
<td>8 (40)</td>
<td>18 (78)</td>
</tr>
<tr>
<td>At 12 months† (%)</td>
<td>7 (35)</td>
<td>13 (56)</td>
</tr>
<tr>
<td>Completely stopped PPI therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 6 months* (%)</td>
<td>0 (0)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>At 12 months† (%)</td>
<td>0 (0)</td>
<td>4 (17)</td>
</tr>
</tbody>
</table>

* At 6 months, no data were available for 3 and 4 patients in the RF and in the control group, respectively (see Methods).
† At 12 months, no data were available for 3 and 6 patients in the RF and in the control group, respectively (see Methods). Missing patients were considered as failures (inability to stop or decrease PPI therapy).
DISCUSSION

The results of this randomized, prospective study show that compared to a classical PPI maintenance strategy, after RF therapy, a significantly higher proportion of patients were able to decrease PPI use or even to stop PPI therapy without losing QOL. No severe complication occurred and both treatments were safe and well tolerated at a 1-year horizon.

Although not blinded, our study has several strengths compared to previous trials. First, we carefully selected reflux patients with truly PPI-dependent GERD. Indeed, during the run-in phase (prior to randomization), we excluded patients with symptoms of highly variable intensity and frequency and those with symptoms controlled by half-dose PPI regimen that we considered not eligible for endoscopic treatment. Although there is no universally accepted definition of ‘PPI dependence’, we tried to exclude the group of ‘over-treated patients’, who are quite numerous in clinical practice as confirmed by our present experience. This is clearly a different group of patients from those enrolled in the sham-controlled trial published by Corley et al.²³ Indeed, in the study of Corley et al., the percentage of patients using PPI at baseline was 88% in the RF group and 72% in the sham-treated group. In contrast, all our patients were initially PPI users and required at least a full standard dose regimen or even a double dose PPI to achieve adequate relief of symptoms. At baseline, a majority of patients were not completely symptom-free, but still experienced intermittent mild symptoms of GERD, despite PPI therapy. We therefore used the term ‘adequate symptom relief’ to describe this situation. Furthermore, both therapeutic arms were well-matched with respect to demographic and reflux disease.

Figure 3. Intensity of (a) regurgitation and (b) heartburn according to a five-point Likert scale, (c) frequency of typical gastro-oesophageal reflux disease symptoms per week and (d) dose of proton pump inhibitor (PPI) required to achieve symptom control in patients on PPI regimen alone (control) and after radiofrequency therapy (RF).
Table 3. Secondary end-points: assessment of symptom intensity, HR-QOL scores at 6 and 12 months and of 24 h pH study and endoscopy at 6 months (Per-protocol analysis)

<table>
<thead>
<tr>
<th></th>
<th>At 6 months</th>
<th></th>
<th>At 12 months</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control ((n = 16))</td>
<td>RF ((n = 20))</td>
<td>(P)-value</td>
<td>Control ((n = 14))</td>
</tr>
<tr>
<td>Dose of proton pump inhibitor required to achieve symptom control* (mg) (mean ± s.d.)</td>
<td>30 ± 19</td>
<td>12 ± 11</td>
<td>0.01</td>
<td>37 ± 30</td>
</tr>
<tr>
<td>Patients with double dose, (N) (%)</td>
<td>10 (63)</td>
<td>5 (25)</td>
<td>0.02</td>
<td>8 (57)</td>
</tr>
<tr>
<td>Patients on demand therapy, (N) (%)</td>
<td>9 (56)</td>
<td>6 (30)</td>
<td>0.11</td>
<td>8 (57)</td>
</tr>
<tr>
<td>Symptom frequency &lt;3 per week</td>
<td>6 (40)†</td>
<td>16 (80)</td>
<td>0.01</td>
<td>8 (62)</td>
</tr>
<tr>
<td>Symptom intensity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean heartburn score*</td>
<td>2.4 ± 1.4†</td>
<td>2.1 ± 1.0</td>
<td>0.47</td>
<td>2.3 ± 1.5</td>
</tr>
<tr>
<td>Mean regurgitation score*</td>
<td>2.2 ± 1.3†</td>
<td>1.3 ± 0.6</td>
<td>0.01</td>
<td>1.7 ± 1.4</td>
</tr>
<tr>
<td>Mean epigastric burning score*</td>
<td>2.5 ± 1.4†</td>
<td>1.4 ± 0.9</td>
<td>0.01</td>
<td>2.0 ± 1.4</td>
</tr>
<tr>
<td>HR-QOL scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF-36 Mean standardized physical component*</td>
<td>49 ± 7†</td>
<td>48 ± 8</td>
<td>0.81</td>
<td>40 ± 10</td>
</tr>
<tr>
<td>Mean standardized mental component*</td>
<td>45 ± 12†</td>
<td>51 ± 9</td>
<td>0.20</td>
<td>50 ± 7</td>
</tr>
<tr>
<td>REFLUX-QUAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global score*</td>
<td>68 ± 21†</td>
<td>75 ± 21</td>
<td>0.43</td>
<td>77 ± 18</td>
</tr>
<tr>
<td>Daily life *</td>
<td>79 ± 20†</td>
<td>80 ± 22</td>
<td>0.86</td>
<td>82 ± 21</td>
</tr>
<tr>
<td>Social life*</td>
<td>73 ± 31†</td>
<td>77 ± 21</td>
<td>0.96</td>
<td>77 ± 30</td>
</tr>
<tr>
<td>Well being*</td>
<td>70 ± 21†</td>
<td>82 ± 22</td>
<td>0.05</td>
<td>79 ± 19</td>
</tr>
<tr>
<td>Mental health*</td>
<td>55 ± 25†</td>
<td>70 ± 27</td>
<td>0.13</td>
<td>67 ± 25</td>
</tr>
<tr>
<td>Fears*</td>
<td>60 ± 31†</td>
<td>79 ± 18</td>
<td>0.03</td>
<td>68 ± 22</td>
</tr>
<tr>
<td>Sleeping*</td>
<td>72 ± 25†</td>
<td>71 ± 19</td>
<td>0.87</td>
<td>81 ± 23</td>
</tr>
<tr>
<td>Feeding*</td>
<td>60 ± 29†</td>
<td>66 ± 26</td>
<td>0.56</td>
<td>73 ± 30</td>
</tr>
<tr>
<td>24 h pH-study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oesophageal acid exposure</td>
<td>9/3‡</td>
<td>17/1‡</td>
<td>0.27</td>
<td>–</td>
</tr>
<tr>
<td>Total time pH &lt;4 (%)*</td>
<td>8.8 ± 6.1</td>
<td>11.4 ± 6.3</td>
<td>0.11</td>
<td>–</td>
</tr>
<tr>
<td>Number of reflux episodes &gt;5 min*</td>
<td>4 ± 4</td>
<td>7 ± 6</td>
<td>0.12</td>
<td>–</td>
</tr>
<tr>
<td>Duration of reflux episodes (seconds)*</td>
<td>78 ± 53</td>
<td>87 ± 39</td>
<td>0.59</td>
<td>–</td>
</tr>
<tr>
<td>Symptom index (%) *</td>
<td>52 ± 45</td>
<td>67 ± 30</td>
<td>0.38</td>
<td>–</td>
</tr>
<tr>
<td>Endoscopy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oesophagitis (%)</td>
<td>7 (54%)§</td>
<td>10 (53%)§</td>
<td>0.97</td>
<td>–</td>
</tr>
<tr>
<td>Oesophagitis A/B</td>
<td>5/1</td>
<td>5/5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Oesophagitis C/D</td>
<td>1/0</td>
<td>0/0</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Control group: proton pump inhibitor regimen alone; RF: Radiofrequency energy delivery; HR-QOL, health-related quality of life.
* Values are expressed as mean ± s.d.
† One missing value.
‡ Four patients in the control arm and two in the RF arm declined pH assessment.
§ Three patients in the control arm and one in the RF arm declined endoscopy.
characteristics (Table 1). The therapeutic needs were also carefully analysed using a standard protocol for dose reduction and withdrawal of PPI therapy based on the self-assessment of symptom relief by the patient. The primary endpoint was based on the patient’s ability and willingness to stop or decrease PPI use without deterioration of symptom control. We also included several secondary endpoints in our trial design, such as systematic pH monitoring and endoscopic assessments at baseline and at 6-month follow-up visits. Finally, we analysed results in the ITT cohort, not only in the PP group of patients. The results of this different analysis were robust and consistently showed an effect of RF on both the primary outcome and several symptoms and HR-QOL scores.

Our study has several limitations inherent to its un-blinded design. Hence, a placebo effect may have contributed to the substantial decrease in the proportion of patients requiring continuous PPI maintenance in both arms, especially in the active one. However, there was a trend towards an increase in symptom severity in the control arm, but not in the RF group, which suggests that control patients actually made efforts to reduce PPI use, despite our recommendations to prioritize maintenance of an adequate symptom relief. In contrast, after RF, the symptom scores and HR-QOL remained stable or even improved, despite the PPI reduction or withdrawal. It is therefore tempting to speculate that the proportion of patients requiring PPI maintenance would in fact have been higher than the 50% reported in the control arm, if the patients had been able to achieve the same level of symptom relief as at baseline. Furthermore, it should be acknowledged that the sham-procedure recommended to ensure blindness of endoscopic trials in GERD also has some drawbacks, as patients may eventually identify the nature of treatment administered, especially when specific adverse effects occur. In France, therapeutic endoscopic procedures are always performed under general anaesthesia and Ethical Committees would not accept general anaesthesia for sham-therapy. Finally, the study was interrupted prematurely because of the decision of Curon Ltd to stop the commercialization of Stretta devices. This decision to stop the trial did not take into consideration the negative results of previous studies on endoscopic treatment of GERD; on the contrary, we were aware of another positive trial of RF (unpublished; Jan Tack, personal communication). We did not have any discussion with Curon before they decided, independently, to stop the commercialization of their device. Such a situation may increase the risk of a type II error, which is obviously not the case in this study in which highly significant differences were observed, despite the relatively small samples. Concerning the lack of effect of RF on OAE, a significant difference with a larger sample size would be very unlikely, as the change was minimal after RF and actually smaller than the spontaneous variability observed in the control arm.

The successful outcome rate of RF in our study is in accordance with that reported in uncontrolled trials conducted in the USA, Puerto Rico and Europe. A significant reduction in GERD symptoms and a better QOL compared with the sham-treated group have also been reported after 6 months by Corley et al. A better outcome after RF than after sham-procedure has also been observed at a 3-month follow-up in another, as yet unpublished, controlled trial carried out in Belgium (J Tack, personal communication). However, contrary to our findings, in the American trial, the difference in the proportion of PPI users between the control and the active therapeutic arms at the end of the study was not statistically significant; one plausible explanation may be that patients were less frequently PPI-dependent at baseline and that reduction occurred in both arms making it difficult to show a statistical difference. In our patients, reflux disease was probably more severe than in Corley’s trial and it is worth noting that the number of patients who were able to stop completely PPIs after RF was actually very low (three at six and four at 12 months, respectively). This discrepancy with previous studies is likely to reflect the more stringent criteria used in our trial to select truly PPI-dependent patients. Moreover, the clinical relevance of the reduction in PPI use after RF.
should be discussed with respect to the general safety of this class of drugs and the rapid development of generic drugs, which may dramatically reduce the cost of maintenance therapy in GERD. Another concern with RF is the limited (if any) efficacy of RF on oesophageal lesions. Indeed, at 6 months, endoscopic evidence of oesophagitis was more prevalent than at baseline in both groups, with no significant difference between the two arms. This is in agreement with data reported by other authors.23 Finally, one should consider the duration of effect of RF. Indeed, a sustained effect has been reported even after a single procedure and benefit has been observed after a follow-up of as long as 4 years.20, 21 In our trial, at 12 months of follow-up, there was still a numerical advantage for RF over PPI-alone strategy, but the difference did not reach statistical significance (Table 2) and several patients relapsed or developed oesophagitis (Table 3). However, our 1 year data are difficult to interpret because of the relatively small number of patients remaining in the trial.

Several mechanisms have been proposed to explain RF effects in GERD, including inhibition of transient lower oesophageal sphincter relaxations and remodelling of the cardiac region leading to reduction in reflux and acid injury of the oesophageal mucosa.16, 31, 32 Our study was not designed to explore mechanistic aspects of this procedure. However, no significant change in OAE was noted between baseline and 6 months after randomization. This finding is consistent with the results of Corley et al.,23 but at variance with other studies.14, 15, 17, 18 Regarding the mechanism of action of RF on symptoms of GERD, an interesting hypothesis is that RF could induce nerve ablation resulting in decreased oesophageal sensitivity. For example, a decrease in oesophageal sensitivity to acid infusion has been demonstrated by Arts et al. 6 months after RF procedure.33 In our study, one could speculate that the absence of worsening of GERD symptoms in the RF group while reducing their PPI use might be explained at least partly by some effect on neural pathways. However, we did not perform a Bernstein perfusion test to explore this hypothesis further.

We did not observe any severe adverse event related to the procedure in the RF group. The Stretta system was approved in the US in 2000 by the Food and Drug Administration and classified as a class II (moderate risk) device. The significant adverse event rate was around 2.2% in the first 6 months of commercial use, and then decreased to approximately 0.1%.34 The advantage of RF over other endoscopic procedures is that it is relatively simple to standardize this technique, which does not require special skills in endoscopy. It is therefore an easy-to-implement technology, well adapted for multicentre trials where standardization is required despite the high number of endoscopists involved. In the future, the development of RF is uncertain, but not necessarily definitively compromised, especially with respect to the consistently positive results reported in three controlled trials (Tack, and the present study).23 Moreover, all of these data show that endoscopic treatment of GERD is feasible and safe, at least with some procedures.

**ACKNOWLEDGEMENTS**

Declaration of personal interests: J. P. Galmiche has served as a speaker, a consultant and an advisory board member for AstraZeneca, Given Imaging, Pentax, Janssen-Cilag, Sanofi, Nycomed and has received research funding from AstraZeneca, Given Imaging, Janssen-Cilag France and Negma-Gild. F. Zerbib has served as a speaker and a consultant for AstraZeneca, Janssen-Cilag, Sanofi and has received research funding from AstraZeneca, Janssen-Cilag France, Sandhill, Addex and Nycomed. P. Ducrotte has served as a speaker for AstraZeneca and Janssen-Cilag and has received research funding from Beaufour Ipsen Pharma and Sanofi. F. Ducrot has worked on the development of Janssen Pharmaceutical gastrointestinal drugs up to 1985, and has occasionally served as a speaker for AstraZeneca since. S. Bruley des Varannes has served as a speaker and a consultant for AstraZeneca, Janssen-Cilag, Sanofi, and has received research funding from AstraZeneca, Janssen-Cilag France, Medtronic and Danone. Declaration of funding interests: This work was supported in part by the Société Nationale Française de Gastro-Entérologie (SNFGE), INSERM and CHU of Nantes. The study was conducted independently of Curon Ltd with no interference of this company in the trial design or analysis of results.
REFERENCES


3 Chiba N. Proton pump inhibitors in acute healing and maintenance of erosive or worse esophagitis: a systematic overview. *Can J Gastroenterol* 1997; 11: 66B–73B.


