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Randomised clinical trial: transoral incisionless fundoplication vs. sham intervention to control chronic GERD

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SUMMARY

Background
Until recently only two therapeutic options have been available to control symptoms and the esophagitis in chronic gastro-oesophageal reflux disease (GERD), i.e. lifelong proton pump inhibitor (PPI) therapy or anti-reflux surgery. Lately, transoral incisionless fundoplication (TIF) has been developed and found to offer a therapeutic alternative for these patients.

Aim
To perform a double-blind sham-controlled study in GERD patients who were chronic PPI users.

Methods
We studied patients with objectively confirmed GERD and persistent moderate to severe GERD symptoms without PPI therapy. Of 121 patients screened, we finally randomised 44 patients with 22 patients in each group. Those allocated to TIF had the TIF2 procedure completed during general anaesthesia by the EsophyX device with SerosaFuse fasteners. The sham procedure consisted of upper GI endoscopy under general anaesthesia. Neither the patient nor the assessor was aware of the patients' group affiliation. The primary effectiveness endpoint was the proportion of patients in clinical remission after 6-month follow-up. Secondary outcomes were: PPI consumption, oesophageal acid exposure, reduction in Quality of Life in Reflux and Dyspepsia and Gastrointestinal Symptom Rating Scale scores and healing of reflux esophagitis.

Results
The time (average days) in remission offered by the TIF2 procedure (197) was significantly longer compared to those submitted to the sham intervention (107), $P < 0.001$. After 6 months 13/22 (59%) of the chronic GERD patients remained in clinical remission after the active intervention. Likewise, the secondary outcome measures were all in favour of the TIF2 procedure. No safety issues were raised.

Conclusion
Transoral incisionless fundoplication (TIF2) is effective in chronic PPI-dependent GERD patients when followed up for 6 months.
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INTRODUCTION

The need for a long-term treatment in many patients with gastro-oesophageal reflux disease (GERD) has become increasingly evident during the past 20 years. Although the pathogenesis of GERD is complex and multifactorial, the likelihood of developing GERD increases with the severity of anatomical change and dysfunction of the gastro-oesophageal junction (GOJ), which represents the primary defence against reflux of gastric content into the oesophagus. It is generally recognised that the restoration of the GOJ competence at the anatomic, mechanic and physiological levels is critical for an effective long-term treatment of GERD.[1–4] In the area of medical therapy for GERD proton pump inhibitors (PPIs) have become the therapy of choice, providing improved healing and symptom control compared with other medical therapies. These effects are achieved without detectable effects on the GOJ patency mechanisms.[5, 6] For a substantial proportion of chronic GERD patients, lifelong daily PPI administration is required to control the clinical manifestations of the disease. Until now there has been one well-established therapeutic alternative for these patients, i.e. laparoscopic anti-reflux surgery (LARS).[7–10] The problem with LARS is that it is generally considered too invasive, exposing each individual patient to a small but not negligible risk of morbidity and even mortality. In addition, anti-reflux surgery is followed by some unavoidable mechanical side-effects, which are basically impossible to predict for each individual patient before the surgical intervention.[11–13]

In an attempt to develop a procedure that mimics anti-reflux surgery in constructing a fundoplication at the GOJ by restoring the angle of His and reducing a small hiatal hernia with few side-effects, a Transoral Incisionless Fundoplication (TIF) procedure has been developed.[14–17] The EsophyX device with SerosaFuse fasteners (EndoGastric Solutions, Inc., Redmond, WA, USA) was designed to reconstruct the GOJ through an anterior partial fundoplication with tailored delivery of multiple fasteners during a single-device insertion. The published clinical series to date suggest that the TIF2 procedure is effective in eliminating symptoms, decreasing the need for daily PPIs, normalising oesophageal acid exposure, increasing lower oesophageal sphincter resting pressure, and promoting healing of oesophagitis in 80% of patients with chronic GERD. When applied to the appropriate patients, TIF resulted in a durable reduction of hiatal hernias and effective reconstruction of the anti-reflux competency of the GOJ.[14–18] There are two fundamentally important issues related to the comprehensive evaluation of the true efficacy of endoscopic interventions in GERD.[19] First, we have to recognise the huge placebo effect of a surgical or endoscopic procedure, necessitating the use of a double-blind, sham-controlled study design. Moreover, when GERD patients are recruited into similar studies, the continued need for PPI has been used as a marker of efficacy of the actual intervention. This is in fact a most dubious efficacy variable. Many patients are prescribed PPI over a long period of time and when carefully investigated for the true presence of the disease, GERD cannot be objectively documented in an astonishingly large proportion.[20–22] In addition, many GERD patients are routinely prescribed PPI without titrating to the lowest effective daily long-term dose of the respective PPI. Consequently, whenever the need for PPI shall be used in clinical trial settings, to evaluate surgical and endoscopic interventions, every patient enrolled has to go through a 'run-in phase' where the real need for daily PPI, to control symptoms, can be documented. Accordingly, as part of a comprehensive and stepwise evaluation strategy for the clinical use of TIF, we performed a double-blind, sham-controlled study in GERD patients who were found to require chronic PPI when assessed through the history and the recurrence of symptoms during the 'run-in phase' without PPI.

PATIENTS AND METHODS

The study population consisted of patients from five European centres with chronic GERD symptoms and without severe anatomic deterioration of the GOJ, as evaluated endoscopically before study procedures, who consented between January 2011 and January 2013 for an endoscopic intervention as an alternative to long-term treatment of PPIs. The following inclusion criteria were applied: age 18–80 years, on daily PPIs for >6 months, documented 'PPI-dependent' (see below), persistent GERD symptoms without PPI therapy (during the titration phase of the study), evidence of *two* or more of the following while *off* PPI therapy (>10 days), erosive oesophagitis [Los Angeles (LA) grade A, B or C], abnormal ambulatory pH study, moderate to severe GERD symptoms, normal or near normal oesophageal motility (by manometry or impedance). The patient had to be willing to cooperate with post-operative dietary recommendations and assessment tests and to sign informed consent.

For this particular study, we adopted the following exclusion criteria; body mass index (BMI) >35, Hill

grade IV, hiatal hernia >3 cm, oesophagitis LA grade D, oesophageal ulcer, oesophageal stricture, Barrett's oesophagus (Prague: C > 1, M ≥ 2), oesophageal motility disorder, severe gastric paralysis, pregnancy or plans for pregnancy in the next 12 months, immunosupressive therapy, American Society of Anesthesiologists (ASA) >2, portal hypertension and/or varies. Moreover, a history of *any* of the following: respective gastric or oesophageal surgery, cervical spine fusion, Zenker's diverticulum, oesophageal epiphrenic diverticulum, achalasia, scleroderma or dermatomyositis, eosinophilic oesophagitis, cirrhosis or coagulation disorders precluded from enrolment.

All patients had a history of PPI treatment >6 months to control GERD symptoms. A 2-month run-in period was allowed for testing the lowest possible dose of PPIs that controlled GERD symptoms. The dose reduction investigation had to be completed before final enrolment into the trial. During this titration part of the pre-enrolment phase, the duration of each dose of respective PPI had to last for at least 2 weeks. Attempts were made to titrate the dose downwards until moderate to severe GERD symptoms emerged and continued for at least 3 days. If 'half dose' (corresponding to 20 mg omeprazole) was taken per day and considered sufficient to control GERD symptoms, the patient was eligible for inclusion. If LA grade C oesophagitis was present at the investigational endoscopy, no further dose reduction of PPI was required.

The use of PPIs plus other GERD medication was recorded in a medication diary. The incidence of anticipated and unanticipated serious and non-serious adverse events was recorded.

There were no changes to study methods after trial commencement. All patients were blinded and treated equally before and after the procedure. Likewise, the assessor was unaware of the patients' group affiliation, securing a double-blind study design.

Study end points

The primary endpoint in the study was the time to 'treatment failure', during the first 6 months after intervention.

The composite endpoint, treatment failure, was defined as follows: The need for PPI treatment to control reflux disease and was assessed at clinic visits when the question was asked 'Do you have sufficient control of your heartburn and acid regurgitation?'. If the answer was no, and the patient stated there was a need to return to a daily single-dose of PPIs, and the reintroduction of medical therapy was followed by symptom control, the patient was classified as a 'treatment failure'.

The patient was also classified as a 'treatment failure' if; there were post-interventional complaints requiring medical action, post-operative death within 30 days after TIF, moderate or severe dysphagia requiring further treatment or reoperation. However, one dilatation was allowed in case of functional stenosis. 'Treatment failure' prevailed if at least one of the following criteria were fulfilled: moderate or severe heartburn and/or acid regurgitation during the last 7 days before the respective visit, oesophagitis of at least grade B at endoscopy, requirement of continuous PPI treatment for more than 8 weeks to control reflux symptoms or need for a re-intervention.

The secondary outcome measures were: frequency and intensity of GERD symptoms assessed by the Quality of Life in Reflux and Dyspepsia (QOLRAD) questionnaire and Gastrointestinal Symptom Rating Scale (GSRS), PPI usage, oesophageal acid exposure, healing of reflux oesophagitis, geometry of GOJ (Hill grading) and the side-effects of the respective intervention.

In case of symptom control, endoscopy and ambulatory 24 h pH-metry were scheduled at the 6 month follow-up visit, otherwise determined by the recrudescence of relevant symptoms.

At the endoscopy, the diagnosis of oesophagitis was scored according to the LA classification. The presence of a hiatal hernia and the assessment of its size were based on the distance from Z-line to diaphragmatic impression measured in cm at retraction of the endoscope with little-to-no insufflation of air.

Geometrical aspects of the TIF valves were assessed by evaluating its: *length*, defined as the length in cm from the apex of the fundus to the valve lip; *circumference*, defined as the distance in degrees between the two most distant fasteners; *adherence* to the endoscope defined as tight, moderate or loose.

The GOJ was graded using the *Hill gastroesophageal* flap-valve classification,[23] defining *grade I* by the presence of a prominent tissue fold surrounding the endoscopic shaft; *grade II* by the presence of a moderately prominent tissue fold which rarely opens with respiration and closes promptly; *grade III* by a barely present fold which fails to close around the endoscope; and *grade IV* by the lack of a muscular fold with lumen of oesophagus staying open all the time allowing the squamous epithelium to be viewed from below.

The TIF2 procedure

Each TIF procedure was conducted by a team of two physicians under continuous visualisation following a standard TIF2 protocol. Antibiotic prophylaxis was administered during induction of general anaesthesia (nasal intubation and anti-emetic protocol; dehydrobenzoperidol, dexamethasone, ondansetron, metoclopramide).

Each procedure was started with an endoscopic examination of the oesophagus, stomach and duodenum, where after the TIF2 EsophyX device with SerosaFuse fasteners (EndoGastric Solutions, Inc) was inserted transorally through a bite-block into the oesophagus and stomach with the patient in left lateral position. Hiatal hernia, if present, was reduced by returning the squamocolumnar junction to its natural position by a supplementary vacuum suction system within the device.

During a single insertion of the device, a valve similar to that created through anti-reflux surgery was created by full-thickness retraction with a helical retractor followed by fixation of the apposed fundus to distal oesophagus with a tissue mold and subsequent deployment of one set of fasteners at each position circumferentially, 1–3 cm above the Z-line, resulting in an approximately 270° anterior fundoplication. The quality of the created valve was evaluated by another endoscopy immediately after the procedure.

The sham procedure consisted of an upper GI endoscopy that was conducted under general anaesthesia in the same type of operating room. The surgical team followed the same steps before, during and after the sham procedure similar to the TIF procedure, except for the transoral insertion of the EsophyX device. The endoscope was manipulated for 20–30 min to simulate TIF procedure and the effect of multiple rotations and manipulations on the oesophagus and cardia caused by the EsophyX device.

Post-interventional follow-up

Patients were discharged from hospital the next day after a complete physical examination and instructed to consume a liquid diet during the first 2 weeks and a soft diet during the following 4 weeks. During weeks 3–6, patients introduced a soft diet consisting of moist fish, canned fruits, bananas, berries, soft eggs, cooked vegetables, mashed potatoes, pasta, moist rice, and cereals (softened in milk). After the 6-week healing time, patients were allowed to incorporate fresh vegetables, meats, bread, citrus and alcohol back into their diet.

Proton pump inhibitors were continued for 6 weeks following the procedure to allow healing of the gastric mucosa around the fasteners and to minimise the consequences of rebound acid hypersecretion. During this 6-week period, the patient received full dose of the PPI for the first 4 weeks followed by half the dosage for the remaining 2 weeks. After 42 days, the patients stopped taking PPIs and other GERD medication. In the event of the recurrence of symptoms during four consecutive days, patients were asked to contact the study coordinator. The nature, intensity and frequency of these symptoms were assessed during in-office visits, and the possible need for GERD medication was determined by the physician.

Patients reporting no improvement in symptoms at 6-month follow-up were offered the option of undergoing revisional surgery. If a patient underwent an alternate surgical therapy for their GERD before the 6-month follow-up, a study exit form was completed. Patients from the sham group classified as 'treatment failure' were offered TIF after completing the 6-month follow-up and followed thereafter according to clinical routines.

Statistics and ethics

A sample size was estimated based on Phase 2 European data.[17] The number of and time to treatment failure at 6 months after initiation of therapy, were illustrated graphically by Kaplan–Meier remission curves. These were compared statistically using the log rank test. In a post hoc analysis, mean scores of GI symptoms (None = 0, Mild = 1, Moderate = 2 and Severe = 3) up to 6 months were compared using a two-sided, two sample *t*-test. Changes from the randomisation value to the average of the 1 and 6 months values of the GSRS reflux dimension scores and QOLRAD scores were compared using analysis of variance (ANOVA) with values from the randomisation visit as covariate. The Fisher's exact test was used to compare the proportions of clinically successful TIF and Sham patients. Results with a two-sided test, a $P < 0.05$ was regarded as statistically significant. Adverse event rates were compared between TIF and Sham by Fisher's exact test. Statistical analysis was carried out using JMP 11.0 (SAS, Cary, NC, USA) statistical program.

All individual centres obtained Ethics committee and Health Authorities approvals and signed written informed consents from participating patients before enrolment. Patients were randomly assigned to either the TIF Procedure or the sham arm. Block randomisations,

with a block size of 6 (3 to TIF and 3 to Sham), was carried out separately in each of the site by an independent statistician and assigned to each consecutive patient using either sealed envelopes or an electronic data capture system. The study was conducted in accordance with the Good Clinical Practices and Declaration of Helsinki and appropriately registered.

RESULTS

Patient characteristics

Of 121 screened patients, 77 (63.6%) were excluded (Figure 1). Almost one quarter of screened patients (19/77, 24.6%) declined to participate due to a concern of being randomised to the sham group. Forty-four patients were eventually randomised, with an equal distribution between the two study groups, and were analysed as the intent-to-treat (ITT) population.

The baseline and disease-related characteristics of the ITT study population are shown in Table 1, demonstrating the similarity between the groups except for significantly older patients in the sham group.

Procedures

The mean operating time for the TIF2 procedure was 69 min (range, 34–133 min). In one case, due to a malfunction of the first device, a second device had to be reinserted to complete the procedure. A mean of 21 (range, 16–36) fasteners was used to create a 270 (range, 240–300) degrees and a 2.9 (range 2–5) cm long fundoplication, as assessed by immediate post-procedure endoscopy.

Primary and secondary outcomes

The primary outcome measure was the time in remission after the respective interventions. As seen in Figure 2, there was a highly significant difference in favour of TIF2 (average 197 days after TIF2 vs. 107 days after sham), where 13/22 (59%) of the patients were in clinical remission without PPI therapy after 6 months.

Of the total of 15 TIF2 patients endoscoped at 6 months, 12 (80%) were scored as Hill grade I–II compared to only 4 at the pre-procedural investigation. In the sham group no important change was noted (Table 2).

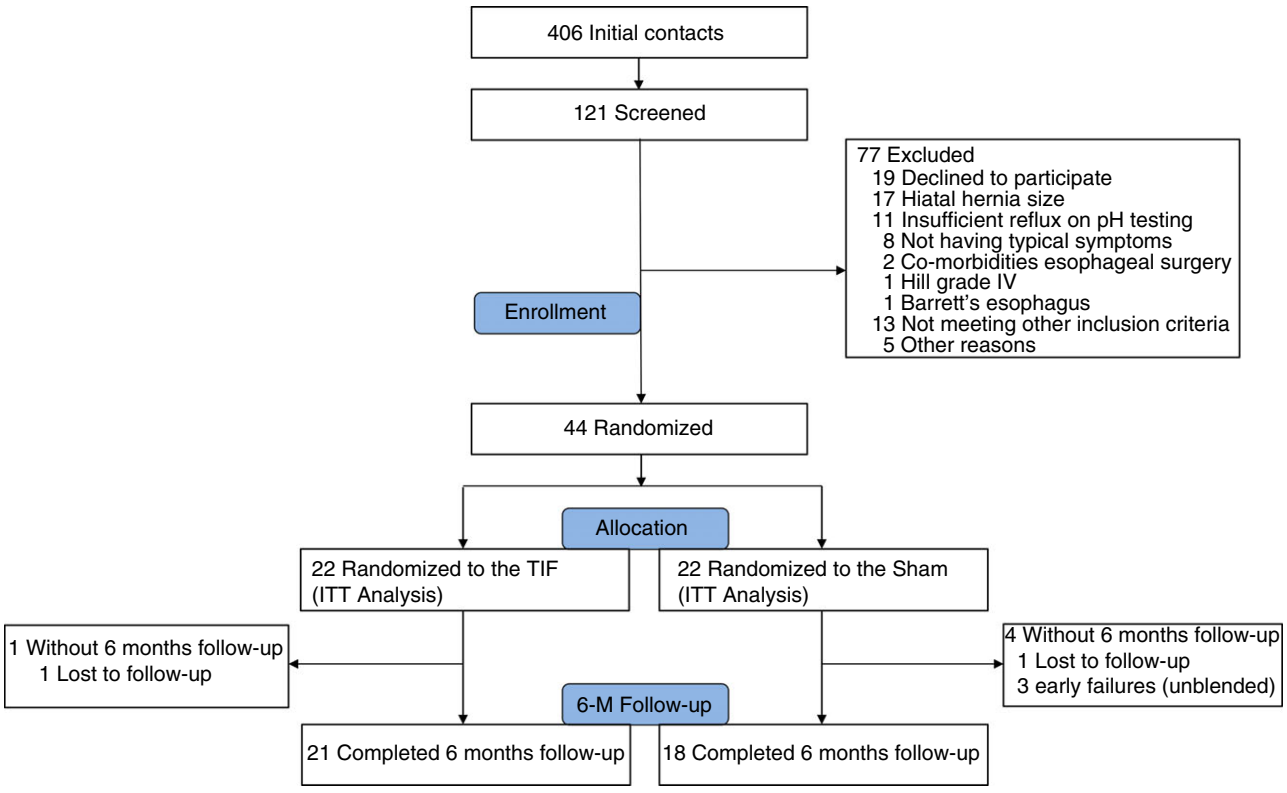

Figure 1 | Flowchart of patients initially screened for participation and those subsequently randomized and followed up according to the protocol.

Table 1 | Demographics and baseline characteristics of patients allocated to either TIF or Sham intervention

Variables	TIF (n = 22)	Sham (n = 22)	P
Female, *n/n* (%)	14/22 (63.6)	6/20 (30)	0.272
Age (years), median (range)	41 (21–67)	62 (31–76)	0.023
Body mass index (kg/m^2), median (range)	26.6 (18.6–33.9)	27.5 (22.5–33.1)	0.382
GERD symptom duration (years) median (range)	10 (2–25)	8 (2–30)	0.723
PPI therapy duration (years) median (range)	6 (2–20)	6 (2–18)	0.916
Oesophagitis (Los Angeles Grade), *n/n* (%)	6/20 (30)	5/17 (30)	>0.999
A	5/6 (83.3)	2/5 (40)	0.242
B	1/6 (16.7)	3/5 (60)	0.242
Hill grade, *n/n* (%)	15/22 (68)	14/22 (64)	>0.999
I	0/15 (0)	1/14 (7)	0.483
II	4/15 (27)	2/14 (14)	0.651
III	11/15 (73)	11/14 (79)	>0.999
Hiatal hernia, *n/n* (%)	17/20 (85)	17/17 (100)	0.234
Axial length ≤2 cm	13/16 (81)	15/17 (88)	0.656
Axial length >2 cm and ≤3 cm	3/16 (19)	2/17 (12)	0.656
Greatest transverse dimension (GTD) ≤2 cm	12/14 (85)	12/15 (80)	>0.999
GTD >2 cm and ≤3 cm	2/14 (14)	3/15 (20)	>0.999
QOLRAD score, median (range)			
On PPIs	6.0 (3.0–7.0)	5.2 (1.96–7.0)	0.112
Off PPIs	4.9 (1.96–6.44)	4.8 (1.80–6.44)	0.848

GERD, gastro-oesophageal reflux disease; PPI, proton pump inhibitor; QOLRAD, quality of life in reflux and dyspepsia.

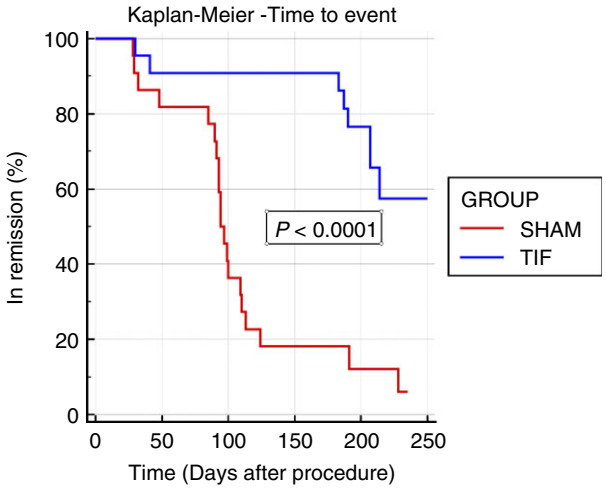

Figure 2 | Time in clinical remission after either transoral incisionless fundoplication (TIF) or sham intervention during the 6 months of follow-up.

Table 2 | The Hill grading[23] of the GOJ at baseline and after 6 months of follow-up in patients randomized to either TIF or sham intervention

	Transoral incisionless fundoplication		Sham procedure	
Hill grade	Baseline	6-month	Baseline	6-month
I	0/15	4/15	1/14	1/10
II	4/15	8/15	2/14	2/10
III	11/15	3/15	11/14	5/10
IV	0/15	0/15	0/14	2/10

Regarding remaining secondary outcome variables the median GERD symptoms scores, as reflected by the QOLRAD estimates, improved significantly at the 6 month follow-up after active intervention [from 4.9 (range 1.96–6.44) at baseline to 6.4 (range 4.38–7) at 6-month follow-up; P = 0.0005], whereas no change was discernible in the sham group [from 4.8 (1.80–6.44) at baseline to 5.2 (4.28–6.88) at 6-months follow-up, P = 0.34]. In the TIF2 group, the median GSRS score improved from 14 (range 10–21) to 10 (6–19) (P = 0.004). Similarly the median reflux dimension of the GSRS score improved from 4 (range 3–7) to 2 (1–5) (P < 0.001). In the sham group, the median GSRS score did not change [from 14.0 (6.3–21.8) to 12.6 (5.9–21.2), P = 0.396]. As an internal control of the GSRS instrument, we observed that the median reflux dimension improved from 4 (3–7) off PPIs to 2.5 (1–4.5) on PPIs (P = 0.004). Of the total 22 TIF2 patients, 13 (59%) were off daily PPI therapy at 6 months, vs. 4/22 (18%) of the sham patients (P = 0.01).

Ambulatory 24 h pH-metry was completed in 15/22 (68%) of TIF2 patients and in 11/22 (50%) submitted to a sham intervention. The changes in each individual patients are depicted in Figure 3 demonstrating a significant reduction in total acid reflux time ($P = 0.003$) by the procedure, whereas no effect was seen in the sham group.

Regarding the question whether TIF2 could 'normalise' acid exposure (i.e. to values with pH below 4 for <4.2% of the 24-h), we observed that 69% of these patients did so, as compared to only 20% among those submitted to a sham procedure ($P = 0.04$).

The clinically significant adverse events at discharge are presented in Table 3. All events resolved at post-operative week 1 visit, except for one TIF2 case where the dysphagia lasted for 3 months but without any need for dilation. None of these events were classified as serious or unanticipated and all resolved without residual effects.

DISCUSSION

Transoral Incisionless Fundoplication has been developed and also found to harbour a potential to offer a therapeutic alternative for chronic GERD patients.[15–17] As part of a comprehensive and stepwise evaluation strategy for the clinical implementation of TIF2, we performed a double-blind, sham-controlled study in GERD patients who were found to require chronic PPI when assessed through the history and the recurrence of symptoms during the 'run-in phase' without PPI. The time to recurrence (treatment failure) after the TIF2 procedure was significantly longer as compared to those submitted to the sham intervention. Thirteen of twenty-two (59%) of the chronic GERD patients remained in clinical remission by the active intervention. In this context it has to be highlighted that the composite outcome measure presently applied has not been frequently used in clinical research practice.[7, 8] This may be problematic as a complete and comprehensive assessment of a specific therapeutic intervention has to take into account a variety of variables and the clinical relevance and internal balance between those can sometimes be both difficult and may even be partly artificial. Indeed, we again found this composite outcome measure, entitled 'treatment failure', to be very useful. Moreover, the statistical analysis of this outcome parameter can then be comprehensively completed by the use of survival statistics.

The secondary outcome measures were: frequency and intensity of GERD symptoms assessed by QOLRAD and GSRS questionnaires, PPI usage, oesophageal acid exposure and geometry of GOJ (Hill grading). Regarding the endoscopic assessment of the distal squamous epithelium of the oesophagus we experienced two issues. One was the limited number of patients accepting a second endoscopy and secondly, many investigators noticed some tissue reaction in the surroundings of the fasteners which sometimes was interpreted as a sign of mucosal inflammation. Moreover, it has to be recognised that the presence of the marks behind the fasteners make the blinding of the endoscopic assessment of the flap valve less robust and may introduce unintentioanl bias.

Table 3 | Moderate to severe adverse events which were by the investigators considered to be clinically significant in patients randomised to either TIF or sham intervention

Adverse events, *n* (%)	TIF (*n* = 22)	Sham (*n* = 22)	*P*
Dysphagia	4 (18)	2 (10)	NS
Bloating	4 (18)	2 (10)	NS
Flatulence	2 (9)	1 (5)	NS
Post-operative epigastric and abdominal pain	10 (45)	1 (5)	NS
Musculoskeletal pain (left shoulder)	3 (14)	0 (0)	NS
Vomiting	1 (5)	0 (0)	NS
Diarrhoea	0 (0)	1 (5)	NS

NS, not significant; TIF, transoral incisionless fundoplication.

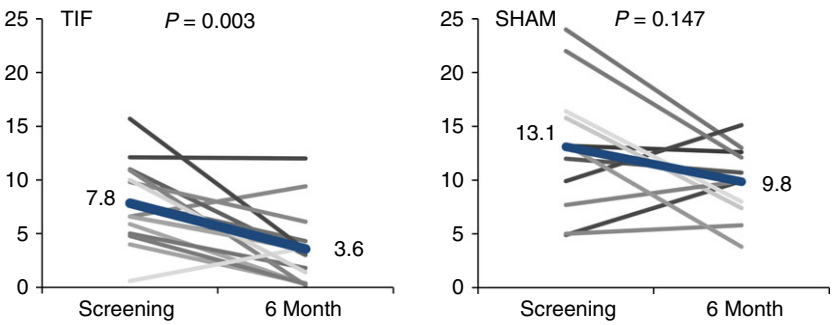

Figure 3 | Total acid exposure in % of the ambulatory intraesophageal 24-h pH recordings performed at baseline and after 6 months post-therapy in the active intervention group (TIF) and in the sham group.

Otherwise, these secondary outcome measures were all in favour of the TIF2 procedure. We observed no safety issues raised by the use of the active intervention.

The present results reinforces the outcome of two previously published clinical trials.[24, 25] One recent US trial applied a design quite similar to the present one, although placebo and omeprazole treatment was added after the respective interventions. Again this was a larger, sham-controlled study and the 6 months follow-up data were similar to those currently presented. In another randomised open-label trial, comparing TIF and PPI therapy, the advantage of TIF intervention was clarified as compared to continued PPI therapy when studied during a 6 month period.[24] Therefore, it can now be concluded that transoral incisionless fundoplication (TIF2) offers chronic GERD patients, being on long-term treatment with PPI, an effective therapeutic alternative. In fact we can also conclude that the level of scientific proof of its efficacy and therapeutic gain surpasses anything which is available outside the area of traditional laparoscopic anti-reflux surgery.[26, 27]

The only device available over the past 5 years that is capable to endoscopically create an anti-reflux valve is the EsophyX device. As more experience has been gained with the procedure, outcomes seem to have improved and the number of complications decreased. An important experience gained is that procedures using fewer fasteners were followed by suboptimal clinical efficacy.[14–16] Accordingly, we used a mean of 21 fasteners. In the trials comparing PPI treatment with TIF2 beneficial effect were demonstrated for the TIF2 over PPI in controlling troublesome GERD symptoms, with a normalisation of intra-oesophageal pH off PPI after TIF2 in 59% of the patients. Similar pH normalisation was achieved with high-dose PPI, but GERD symptoms, particularly regurgitation and atypical symptoms, seemed to be better controlled by TIF2 than by high-dose PPI.[28, 29] Future refinements of the procedure have also to document its capacity to achieve an even better control of reflux into the oesophagus, to which is adhered a potential for even better clinical effects.[30]

Another important step in the critical evaluation of the TIF procedure is the long-term follow-up. For medical therapy, 6–12 months of maintenance therapy is usually considered to be long-term, but for a lifelong therapeutic intervention longer follow-up is mandatory. Recent single and multi-institutional prospectively collected case-series with a follow-up of 3 and 6 years, suggested lasting efficacy of the TIF procedure.[31–33] It is, however, of vital importance to carefully and objectively follow these patients in order to comprehensively document the true durability of the intervention. The outcome of a recent single institution, interim analysis of 60 chronic GERD patients randomised to either TIF2 or PPI therapy followed up for 12 months, reported data which questioned the durability of the procedure.[34] In this context, it has to be mentioned that this study design was neither blinded nor sham-controlled and did use a primary outcome variable which was less stringent than in the present study. No doubt the durability of the endoscopic reconstruction of the anti-reflux valve has to be more carefully assessed and similar studies are currently ongoing.

The question is already there whether the TIF2 can fill the 'therapeutic gap' that exists between PPI and laparoscopic fundoplication? In this context it has to be kept in mind that up to 40% of GERD patients have troublesome symptoms, despite adequately dosed PPI.[28, 29] Many of these PPI resistant cases are currently considered and/or referred to LARS. Although this group of patient might be effectively treated with laparoscopic fundoplication, the absence of hiatal hernia or advanced oesophageal disease raises the question whether a less invasive and more calibrated treatment might better fill this gap? The TIF2 intervention seems to offer particular benefits in improving the symptom of regurgitation.[25] Considering the absence of dysphagia and bloating after TIF2, it would appear that this procedure is an option for patients with troublesome regurgitation, as well as for patients with troublesome GERD symptoms in general who wish not to take PPI for a prolonged period of time. The time seems also to be right for a direct head-to-head comparison between TIF and LARS.

The TIF2 procedure with EsophyX, however, is not an ideal option for all patients. Ideal TIF candidates include patients with persistent GERD symptoms without chronic anti-secretory pharmacotherapy and with the following anatomic characteristics: (i) hiatal hernia less than or equal to 2 cm without an enlarged hiatus; (ii) normal oesophageal motility; (iii) abnormal ambulatory pH or evidence of reflux oesophagitis on endoscopy or biopsy; (iv) Hill grade II–III at the GOJ. To develop this therapeutic concept even further, hybrid approaches e.g. laparoscopic reduction of the hiatal hernia and crural repair added to a conventional TIF2 shall be further explored.

In conclusion, TIF is an effective therapeutic alternative for selected chronic GERD patients.

AUTHORSHIP

Guarantor of the article: Lars Lundell.

Author contributions: Lundell, Håkansson, Arnelo, Thorell, Tack, Bruley des Varannes and Cadiere contributed to the design of the study. Lundell was a principal investigator for this research and drafted the manuscript. Håkansson, Montgomery, Cadiere, Rajan, Bruley des Varannes, Lerhun, Coron, Tack, Bischops, Thorell and Arnelo participated in the research and critically revised the manuscript. Lundell and Håkansson were involved in data collection, analyses and interpretation of data. All authors approved the final version of the article.

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