A randomised controlled Trial Of Proton Pump Inhibitor therapy in Throat Symptoms (TOPPITS)

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Abstract

Background

Persistent throat symptoms, such as throat clearing, globus sensation, voice change and catarrh are extremely common. On very limited evidence, they are increasingly attributed to "laryngopharyngeal reflux (LPR)" and treated with proton pump inhibitors (PPIs) in primary and secondary care.

Methods

A double blind placebo controlled UK multicentre phase III trial randomly allocated adults with persistent throat symptoms 1:1 to either 30 mg of Lansoprazole or matched placebo twice daily for 16 weeks, stratified by centre and symptom severity. The primary outcome was patient-reported symptomatic response, measured by the total Reflux Symptom Index (RSI) score at the end of therapy. Secondary outcomes included safety, further symptoms and quality of life measures at 12-months.

Results

346 participants were randomised from 8 UK centres: mean (sd) age 52 (13), 196 (57%) female, 162 (47%) severe symptoms, balanced across randomised groups. Mean RSI scores (95% CI) were similar at baseline- Lansoprazole: 22.0 (20.4, 23.6), placebo: 21.7 (20.5, 23.0). Improvements (reduction in score) were observed in both groups at 16-weeks: Lansoprazole: 17.4 (15.5, 19.4), placebo: 15.6 (13.8, 17.3) (p=0.096 adjusted by site, severity). There was no statistically significant difference between randomised groups. No significant differences were observed in the secondary outcome measures.

Conclusions

TOPPITS is the largest, definitive trial to assess PPI effectiveness for persistent throat symptoms. It found no advantage of Lansoprazole over placebo in a range of outcomes. The near routine use of PPIs for throat symptoms should be discontinued.

Trial numbers:

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Introduction

Persistent throat symptoms incorporate various common complaints that include: hoarseness, a feeling of a lump in the throat ("globus"), repeated throat clearing, mucus in the throat or "catarrh", cough and throat discomfort. These are a burden to health care providers. The prevalence of globus alone, in middle aged women, is approximately 6%[1] with a lifetime ever population incidence over 40%[2]. A quarter of all patients attending primary care may report significant throat symptom [3]. Many ultimately attend for specialist review in secondary care[4].

Gastroesophageal reflux disease (GERD) affects up to 20% of the Western population and the concept that GERD causes throat and voice symptoms - "laryngopharyngeal reflux" or "LPR" has been increasingly popular for many years [5]. A survey in 2007 showed that 90% of British otolaryngologists believed in the LPR concept, for which over 50% prescribed proton pump inhibitors (PPIs)[6]. Large observational cohort studies point to symptomatic and endoscopic benefit from PPI treatment [7,8]. Meta-analyses of heterogeneous, generally underpowered clinical trials have failed to demonstrate any benefit over placebo[9,10], yet PPIs continue to be the default first line therapy in primary and secondary care.

The Trial of Proton Pump Inhibitors in Throat Symptoms (TOPPITS) aimed to generate definitive evidence on the role of PPIs in the treatment of persistent adult throat symptoms.

Methods

Oversight of the trial

TOPPITS was an investigator-initiated multicentre, randomised, double-blind, placebo controlled trial conducted in 8 hospitals in the United Kingdom. The trial protocol was approved by the regional ethics committee and has been published previously[11]. The trial was independently funded by the Health Technology Assessment (HTA) peer review programme of the National Institute for Health Research. Both an independent Data Monitoring Committee (DMC) and Trials Steering Committee (TSC) provided oversight of the trial. TOPPITS was performed in accordance with the principles of the Declaration of Helsinki. The authors take responsibility for the fidelity of the trial and the accuracy and completeness of the data and analysis.

Patients

Participants were adult patients, newly referred to secondary care otolaryngology clinics with persistent (over six weeks) unexplained throat symptoms, principally: hoarseness, throat pain, globus sensation, throat clearing, post nasal drip or mucus excess, night time unexplained cough or choking. These symptoms were assessed using the Reflux Symptom Index (RSI) patient self-report questionnaire[12], a score commonly utilised and supported with published sensitivity data. However, item nine of the RSI is a composite GERD question covering heartburn (HB), chest pain, indigestion or stomach acid coming up. Item nine was therefore omitted from our eligibility assessment and from baseline stratification, which aimed to balance throat symptom severity between the groups. To be eligible for TOPPITS, patients required a score of 10 or more on the remaining 8 items of the RSI (which we term RSI-HB). Patients were excluded if laryngopharyngeal endoscopy revealed pathology requiring specific treatment, such as vocal cord polyps or malignancy, or if they had a contraindication to receive proton-pump inhibitors (PPIs). Patients currently taking a PPI required a wash-out period of 4 weeks to enter the trial and those taking alginates were required to discontinue these. The complete list of inclusion and exclusion criteria has been published previously[11]. All participants provided written informed consent.

Trial Procedures

The active intervention was a 16-week course of a 30mg twice-daily dose of the PPI Lansoprazole, taken 30 minutes before food. The control group received a 16-week course of twice-daily matched placebo capsules. The allocation was blind to participant and research team staff (double-blind) and was maintained through the trial. A blocked allocation randomisation system (permuted random blocks of variable length) was developed by an independent statistician and used to allocate patients in a 1:1 ratio stratified by centre and baseline severity on the basis of a dichotomised RSI-HB score ($10 \leq$ Mild ≤ 20; Severe > 20). The TOPPITS severity strata were derived from data in prior published RSI datasets [7,8,13,14]. Randomisation was administered centrally via the Newcastle Clinical Trials Unit using a secure web-based system.

Outcome Measures

The primary outcome measure was the total RSI score at 16 weeks after randomisation[12]. The RSI score is a summation of all nine-items, scored on a 6 point Likert scale 0-5, giving a total RSI range of 0-45 (see Supplementary Appendix). A higher score indicates more severe symptoms.

The secondary outcome measures were:

- Adverse events
- Compliance with intervention
- RSI at 12 months from randomisation
- RSI score omitting the GERD item (RSI-HB) (score 0 to 40)
- Two further patient self-report symptom measures, the 34 item Comprehensive Reflux Symptom Score[13] and the 43 item Laryngopharyngeal Health Related Quality of Life (LPR HRQL) within 12-months[14]. For both, higher scores equate to more severe symptoms
- Utility of baseline laryngeal mucosal changes (assessed by a single clinician, blind to the symptom scores) recorded by the Reflux Finding Score (RFS) [15] as a predictor of outcome
- Patient post treatment prediction of allocated intervention

Statistical Considerations

The primary analysis of the primary outcome measure was a multivariable multilevel mixed effect linear regression to compare the RSI at 16 weeks while adjusting for the stratification factors at randomisation: i) centre, as a random effect, and ii) the mild / severe baseline severity as a fixed effect. The primary intention to treat analysis (ITT) was performed on a "compliant" group of patients, as defined by the TSC i.e. those who completed the primary outcome within a 14 to 20 week window, retaining patients in their randomised group. Secondary ITT analyses were performed on the "pragmatic" group i.e. all patients completing the primary outcome. Secondary analyses of the primary outcome also included adjustment for RFS as a continuous measure (investigating non-linear relationships using first order fractional polynomial transformation) and for other important clinical and demographic baseline factors.

Analyses of secondary outcomes followed a similar strategy for questionnaire scores. Safety data were not subject to statistical comparison. Data were analysed using statistical software package (STATA14). A Statistical Analysis Plan, following published guidance[16] was in place prior to comparative analyses. No formal interim analyses were planned.

Target recruitment was 332 patients. A mean difference of 3-points in RSI score at 16 weeks was deemed to be clinically relevant. With an assumed standard deviation of 7.7[17] a mean difference of 3.1 points equates to a standardised mean effect size of 0.4. A total of 332 participants (166 in each arm of the study) were estimated to provide 266 participants (133 in each arm) completing the trial intervention, to be able to detect this standardised effect size with 90% power and 5% significance, allowing for 20% drop out.

Results

Patients

A total of 346 patients, from 1427 initially screened for eligibility, were recruited through 8 UK centres and randomised between April 2014 and February 2017; 172 to Lansoprazole and 174 to placebo (Figure 1). Drop-out was observed as anticipated in the design and was not differential across randomised groups. There were 267 (77%) patients who completed the primary outcome measure at 16 weeks (pragmatic ITT group), 220 within the 14 to 20 week window (compliant ITT group). RSI questionnaires returned at 16-weeks were fully completed. The power to detect the clinically relevant difference in RSI score at 16 weeks was 82% (compliant group) and 89% (pragmatic group).

The compliant ITT group were a representative sample of the trial population in terms of demographics (Table 1): 126 (57%) were female, mean (sd) age 54.5 (13.1), 107 (49%) severe RSI-HB and overall mean (sd) RSI-HB score of 20.0 (7.0), balanced across randomised arms (see Supplementary Appendix for all demographics).

Treatment

In total, 265 of 346 (77%) had information on returned trial medication of whom 262 (99%) were reported to have started treatment, taking at least one capsule. Treatment kits contained a 16-week course of 224 capsules. 111 (42%) of patients reported taking full dose, balanced across randomised groups, while 184 (70%) patients reported taking at least 90% of full dose, balanced across randomised groups. There were 112 adverse events (AE) reported in 74 patients, 80 (71%) of which occurred during treatment: 42 (70%) Lansoprazole and 38 (73%) placebo. One severe AE was probably related to treatment; a rash appearing after taking the allocated treatment.

When asked, post treatment, to predict their allocated intervention, 42% of the Lansoprazole group and 56% of the placebo correctly identified the treatment they had received at the end of the trial period, hence the blinding was maintained.

Primary Outcome Measure

An improvement in RSI (reduction in score) was observed overall in the compliant ITT group at 16 weeks, reducing from mean 21.9 (sd 7.5) at baseline to mean 16.4 (sd 9.9). This improvement was observed in both randomised treatment groups (Table 2, Figure 2). Multilevel mixed effect linear regression of 16-week RSI, adjusted for stratification factors at randomisation (site and RSI-HB severity category) showed baseline RSI-HB to be significantly related to 16-week RSI (Table 3). Patients in the severe severity stratum at baseline are estimated to have eight points higher (worse) RSI score at 16 weeks. There was no statistically significant difference in RSI scores at 16-weeks between randomised groups: Lansoprazole patients are estimated to have scores 1.9 points higher (worse) than placebo (95% CI: -0.3, 4.2, p=0.096) when adjusted for stratification factors.

Secondary analyses of the primary outcome i) in the wider pragmatic ITT group (Supplementary Appendix) ii) when adjusting for other important clinical and demographic baseline factors and iii) analysing RFS as a continuous measure gave similar results with no statistically significant difference in

16 week RSI between the treatment groups, and did not alter the conclusions of the trial. Longer term, the trial concluded that Lansoprazole patients were estimated to have RSI scores at 12 months 2.5 points higher (worse) than placebo (95% CI: -0.1, 5.0, p=0.06, Supplementary Appendix)

Secondary Outcome Measures

Analysis of the RSI-HB demonstrated the Lansoprazole group to have a mean 16-week score 2.4 points higher (worse) than the placebo group: 16.3 (95% CI: 14.5, 18.1) vs 13.9 (95% CI: 12.2, 15.5). The overlapping confidence intervals indicate no statistically significant difference.

The CReSS scores improve (reduce) from baseline to 16 weeks in both randomised treatment groups (see Supplementary Appendix) with overlapping confidence intervals.

The mean LPR HRQL quality of life scores show similar marked improvement at 16-weeks in both randomised treatment groups (see Supplementary Appendix). Multi-level modelling estimated Lansoprazole has on average 2.9 higher (worse) overall LPR HRQL outcome score than placebo (95% CI: -4.3, 10.1, p=0.427).

Reflux Finding Scores at baseline were available for 256 patients in the trial (80% of those in the Lansoprazole arm and 72% in the placebo arm). Mean baseline RFS scores (sd) were 9.7 (4.1) in the Lansoprazole group and 9.2 (3.8) in the placebo group. The baseline RFS scores were not significantly related to the RSI score at 16 weeks using first order fractional polynomial transformations.

Discussion

The TOPPITS trial is the largest, fully powered, double-blind randomised controlled trial to provide definitive evidence of the role of PPIs in treating persistent throat symptoms. In line with the Health Technology and Assessment programme, TOPPITS was a pragmatic design ensuring results are immediately generalizable to the clinical setting. The results demonstrate that Lansoprazole offers no benefit over placebo for patients with persistent throat symptoms. No trends exist in favour of

Lansoprazole. Indeed, patients who received Lansoprazole tended to report worse symptom improvement than those receiving placebo. Treating patients "empirically" with PPIs, in the absence of specialist investigations, represents by far the commonest current scenario for health care practitioners internationally. This practice should now be discouraged through evidence based treatment guidelines.

Prior high quality evidence is lacking in support of PPIs to treat symptoms. The inability of placebo controlled trials to replicate the benefits of PPIs in uncontrolled observational studies of PPIs point to a misattribution of placebo enhanced spontaneous resolution in such single cohort reports[7,8].A systematic review [9] of studies that used PPIs as an empiric treatment modality for suspected LPR identified 14 uncontrolled studies, one un-blinded, non-randomised study with a control group of healthy volunteers and six double-blind, placebo-controlled randomised trials from 1994 to 2004. A lack of common outcome measures, selection bias and or inadequate blinding of the results were among typical limitations. A later meta-analysis [18] included further studies, notably that of Vaezi et al , and concluded that PPI therapy 'may offer a modest but non-significant clinical benefit' over placebo. Subsequent meta-analyses again showed PPI therapy lacked evidence of efficacy in those suspected of LPR. Rather, high placebo response levels suggested a much more complex and multifactorial pathophysiology [10,19]. Very little evidence exists assessing the role of other factors which may reduce reflux, such as diet[20], alginates[17] and lifestyle[21]. The TOPPITS results would support the reinvestment of research into the psychological concomitants of throat symptoms; anxiety, distress, depression and co-existing persistent physical symptoms[22-24].

TOPPITS demonstrates definitively that Lansoprazole does not benefit patients with persistent throat symptoms, over placebo. These findings reasonably extrapolate to other PPIs. TOPPITS does not refute reflux as a cause or contributing factor for some patients' symptoms but the results must surely call into question the now near ubiquitous use of the term "laryngopharyngeal reflux", which has gradually supplanted many other terms such as globus and catarrh, and carries unwarranted etiological connotation. The authors would advocate the non-prejudicial term "persistent throat symptoms" to promote further research into optimum management strategies of these complaints. Whilst reflux of gastric contents

containing pepsin may be implicated in some patients, defining such individuals requires further research. It is probable that reflux does not play a significant role for the vast majority of patients with persistent throat symptoms. Strategies that employ the techniques of reattribution, lifestyle adjustment and behaviour modification of speech or cognitive behavioural therapy [24-28] appear more relevant and a reasonable focus of further research.

Conclusions

Twice daily Lansoprazole offered no symptomatic benefit over matched placebo for patients with persistent throat symptoms. The TOPPITS trial is the largest double-blind, multi-centre randomised controlled trial to date and confirms that the common practice of prescribing PPIs to this patient population should be discontinued.

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Table 1 Baseline demographic data

		All Patients			Compliant ITT group		
Variable		**Lansoprazole n=172**	**Placebo n=174**	**Total n=346**	**Lansoprazole n=102**	**Placebo n=118**	**Total n=220**
Gender	Male	71 (41%)	79 (45%)	150 (43%)	38 (37%)	56 (47%)	94 (43%)
	Female	101 (59%)	95 (55%)	196 (57%)	64 (63%)	62 (53%)	126 (57%)
Age(years)	Mean (SD)	53.5 (13.3)	50.8 (13.9)	52.2 (13.7)	55.3 (12.8)	53.8 (13.4)	54.5 (13.1)
	Range	(21,84)	(20,80)	(20, 84)	(23,84)	(21,80)	(21, 84)
Body Mass Index	Mean (SD)	28.2 (5.9)	28.1 (5.3)	28.1 (5.6)	28.5 (6.7)	28.4 (5.4)	28.5 (6.1)
	Range	(11.3,56.9)	(18.3,49.1)	(11.3,56.9)	(11.3,56.9)	(18.3,49.1)	(11.3,56.9)
Baseline severity RSI-HB	Mean (SD)	20.0 (6.8)	20.1 (6.5)	20.1 (6.6)	20.3 (7.4)	19.8 (6.6)	20.0 (7.0)
	Range	(10,38)	(10,38)	(10,38)	(10,38)	(10,38)	(10,38)
*Severity	Mild	91 (53%)	93 (53%)	184 (53%)	53 (52%)	60 (51%)	113 (51%)
	Severe	81 (47%)	81 (47%)	162 (47%)	49 (48%)	58 (49%)	107 (49%)

* Stratification Factor at Randomisation: Mild (10≤RSI-HB≤20), Severe (RSI-HB>20)

Figure 1 CONSORT diagram

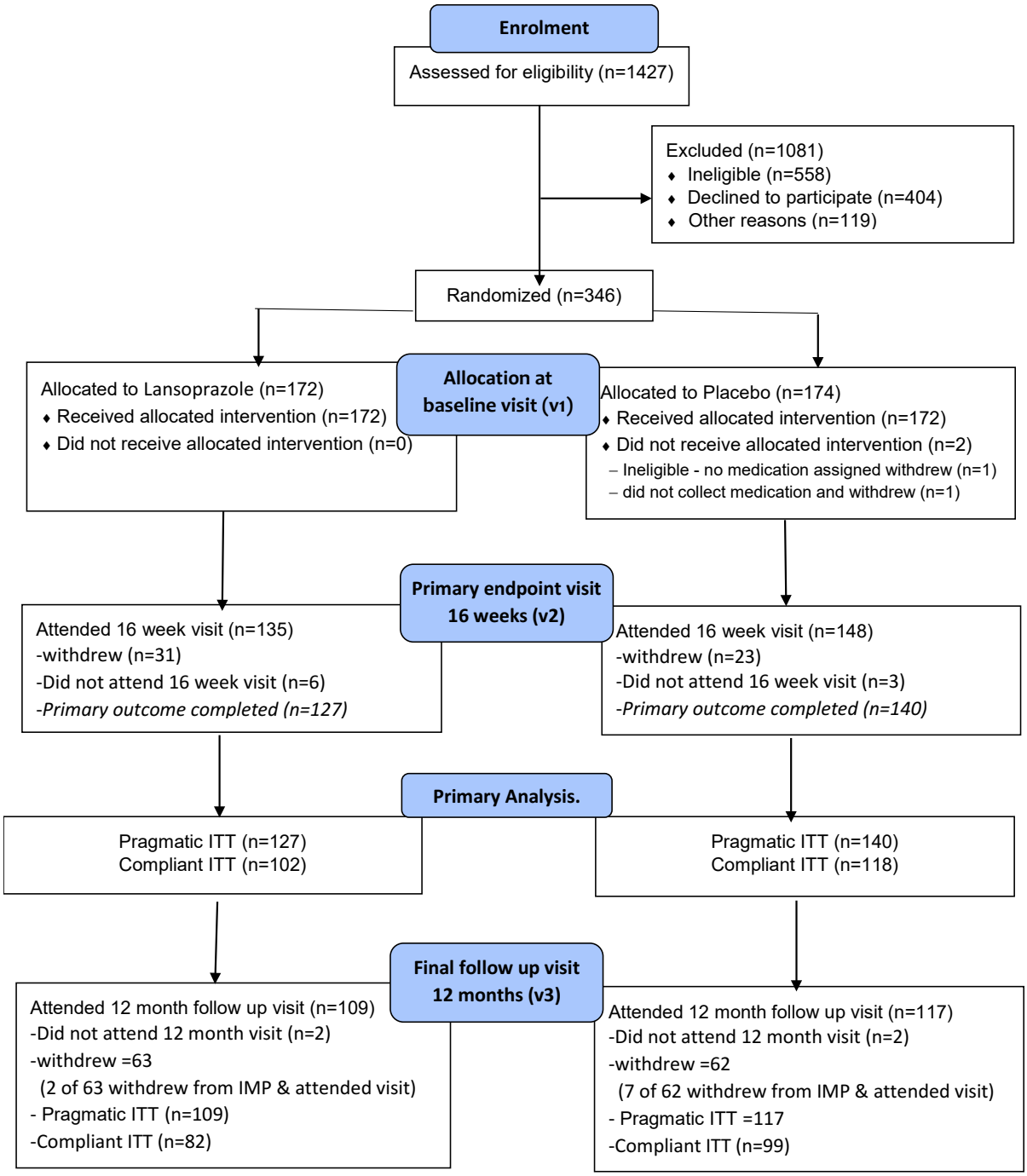

Table 2 Summary of questionnaire outcome scores [mean (95% Confidence Interval)]

			Visit		
Questionnaire	Intervention	n	Baseline	16 weeks	12 months
RSI	Lansoprazole	102	22.0 (20.4, 23.6)	17.4 (15.5, 19.4)	16.0 (13.6, 18.4)
	Placebo	118	21.7 (20.5, 23.0)	15.6 (13.8, 17.3)	13.6 (11.7, 15.5)
RSI-HB	Lansoprazole	102	20.3 (18.8, 21.7)	16.3 (14.5, 18.1)	13.5 (6.0, 22.0)
	Placebo	118	19.8 (18.6, 21.0)	13.9 (12.2, 15.5)	10.0 (5.0, 17.0)
CReSS	Lansoprazole	102	50.3 (44.9, 55.7)	38.9 (33.4, 44.3)	36.6 (29.8, 43.5)
	Placebo	118	51.1 (46.4 ,55.8)	34.7 (29.6, 39.9)	31.8 (26.6, 36.9)
LPR-HRQL	Lansoprazole	102	28.9 (24.5, 33.3)	20.5 (16.1, 25.0)	18.8 (13.7, 23.8)
	Placebo	118	26.5 (22.5, 30.5)	17.1 (13.3, 21.0)	13.9 (10.0, 17.8)

Figure 2 Reflux Symptom Index score at baseline and follow-up visits (median, interquartile range (IQR), upper and lower adjacent values (+/-1.5xIQR) and outlier)

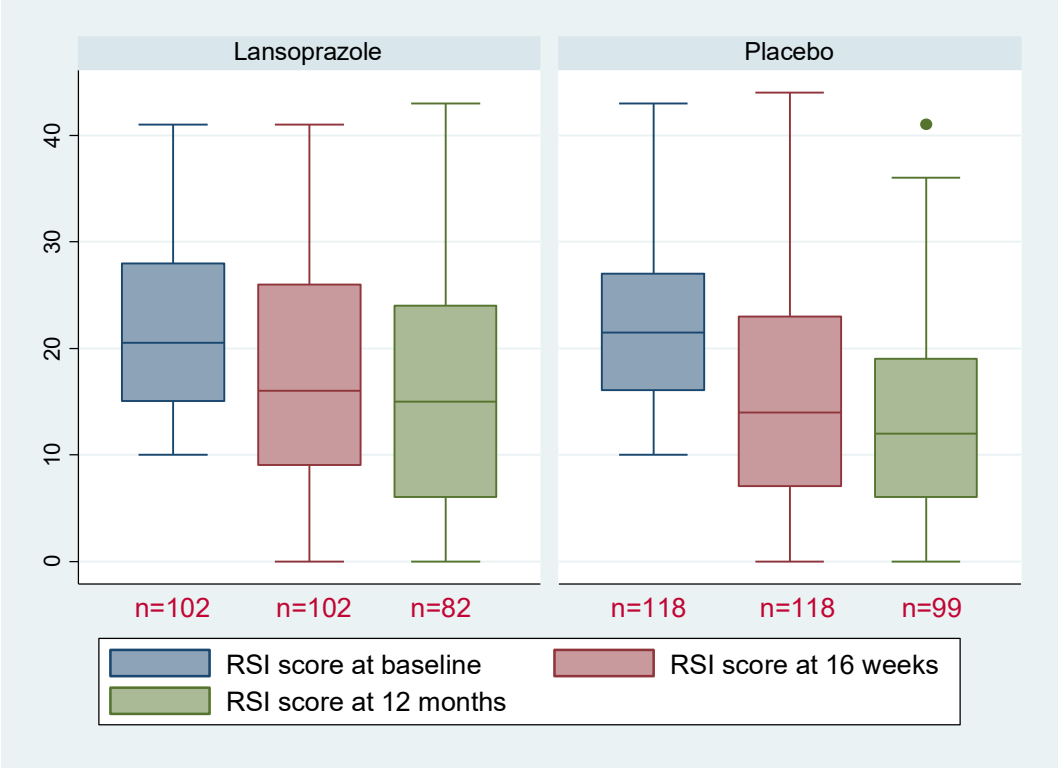

Table 3 Multilevel mixed effect linear regression

Model (n=220)*	β	se (β)	Test statistic	p-value	95% CI (β)	
					lower	upper
Group (ref = Placebo) Lansoprazole	1.929	1.160	1.66	0.096	-0.345	4.203
RSI-HB baseline severity: (ref =Mild) Severe	8.173	1.181	6.92	<0.001	5.858	10.489
Constant	14.349	3.044	4.71	<0.001	8.383	20.315

*Adjusted by Site (Random Effect); se=standard error; CI=confidence interval

The Trial of Proton Pump Inhibitors in Throat Symptoms – Supplementary Appendix

Contents:

Table 1 The Reflux Symptom Index

Permission to use in the trial and reproduce for publication obtained from the authors. The use of the Reflux Symptom Index (RSI) without the 9th item (RSI- Heartburn score, RSI-HB) was devised specifically for TOPPITS.

Within the last MONTH, how did the following problems affect you?

0 = no problem 5 = severe problem

Hoarseness or a problem with your voice	0	1	2	3	4	5
Clearing your throat	0	1	2	3	4	5
Excess throat mucus or postnasal drip	0	1	2	3	4	5
Difficulty swallowing food, liquids or tablets	0	1	2	3	4	5
Coughing after eating or lying down	0	1	2	3	4	5
Breathing difficulties or choking episodes	0	1	2	3	4	5
Troublesome or annoying cough	0	1	2	3	4	5
Sensation of something caught in your throat or a lump in your throat	0	1	2	3	4	5
Heartburn, indigestion or stomach acid coming up	0	1	2	3	4	5

TOTAL		**TOTAL minus heartburn score**	

Table 2 Baseline demographic characteristics and stratification variables, all randomised patients and pragmatic ITT population

		All randomised patients (n=346)			Pragmatic ITT population (n=267)		
Variable		Lansoprazole	Placebo	Total	Lansoprazole	Placebo	Total
Gender	Male	71 (41%)	79 (45%)	150 (43%)	49 (39%)	65 (46%)	114 (43%)
	Female	101 (59%)	95 (55%)	196 (57%)	78 (61%)	75 (54%)	153 (57%)
Age(years)	Mean (SD)	53.5 (13.3)	50.8 (13.9)	52.2 (13.7)	54.8 (12.8)	52.3 (13.7)	53.5 (13.3)
	Range	(21,84)	(20,80)	(20, 84)	(23, 84)	(21, 80)	(21,84)
Body Mass Index (BMI)	n	169	170	339	125	140	265
	Mean (SD)	28.2 (5.9)	28.1 (5.3)	28.1 (5.6)	28.1 (6.3)	28.1 (5.3)	28.1 (5.8)
	Range	(11.3,56.9)	(18.3,49.1)	(11.3,56.9)	(11.3,56.9)	(18.3,49.1)	(11.3,56.9)
Baseline severity RSI-HB	n	171	171	342	127	140	267
	Mean (SD)	20.0 (6.8)	20.1 (6.5)	20.1 (6.6)	20.0 (6.9)	20.0 (6.5)	20.0 (6.7)
	Range	(10,38)	(10,38)	(10,38)	(10,38)	(10,38)	(10,38)
*Severity	Mild	91 (53%)	93 (53%)	184 (53%)	69 (54%)	72 (51%)	141 (53%)
	Severe	81 (47%)	81 (47%)	162 (47%)	58 (46%)	68 (49%)	126 (47%)

* Stratification Factor at Randomisation: Mild (10≤RSI-HB≤20), Severe (RSI-HB>20)

Table 3 Primary outcome measure RSI, pragmatic ITT population

	Baseline (Visit 1)		**16 weeks (Visit 2)**	
	Lansoprazole (N=127)	Placebo (N=140)	Lansoprazole (N=127)	Placebo (N=140)
Median (IQR)	21 (16, 26)	22 (16, 27)	15 (9, 25)	15 (8, 23)
Mean (SD); CI	21.7 (7.4)	21.9 (7.0)	17.1 (9.6); 15.5, 18.8	16.0 (9.5); 14.4, 17.6
Range	(10, 41)	(10, 43)	(0, 41)	(0, 44)

CI = 95% confidence internal about mean

Table 4 Multilevel mixed effect linear regression, pragmatic ITT population

Model (n=267)*	β	se (β)	Test statistic	p-value	95% CI (□)	
					lower	upper
Group (ref = Placebo) Lansoprazole	1.465	1.056	1.39	0.165	-0.604	3.534
RSI-HB baseline severity: (ref =Mild) Severe	7.444	1.071	6.95	<0.001	5.345	9.543
Constant	15.174	3.014	5.03	<0.001	9.267	21.081

*Adjusted by Site (Random Effect); se=standard error; CI=confidence interval

Table 5 Multilevel mixed effect linear regression at 12 months, compliant ITT population

Model (n=185)*	β	se (β)	Test statistic	p-value	95% CI (β)	
					lower	upper
Group (ref = Placebo) Lansoprazole	2.469	1.311	1.88	0.060	-0.100	5.038
RSI-HB baseline severity: (ref =Mild) Severe	8.233	1.314	6.27	<0.001	5.658	10.808
Constant	19.149	4.405	4.35	<0.001	10.515	27.784

Table 6 Comprehensive Reflux Symptom Score total scores at 16 weeks

CReSS	Total (range: 0-170)	
	Lansoprazole	Placebo
n	102	118
Median (LQ, UQ)	36 (15,55)	27.5 (14,48)
Mean (SD)	38.9 (27.7)	34.7 (28.3)
95% CI	(33.4, 44.3)	(29.6, 39.9)
Range (min, max)	(2,140)	(0,158)

Figure 1 Laryngopharyngeal Reflux Health Related Quality of Life