Check for updates

The Laryngoscope
© 2019 The American Laryngological,
Rhinological and Otological Society, Inc.

Systematic Review

Clinical Outcomes of Laryngopharyngeal Reflux Treatment: A Systematic Review and Meta-Analysis

Jerome R. Lechien, MD, PhD, MS; Sven Saussez, MD, PhD; Antonio Schindler, MD, PhD; Petros D. Karkos, MD, PhD; Abdul Latif Hamdan, MD, MPH, FACS; Bernard Harmegnies, PhD; Lisa G. De Marrez, MD; Camille Finck, MD, PhD; Fabrice Journe, PhD; Marianne Paesmans, MSc; Michael F. Vaezi, MD, PhD, MS

Objectives: To investigate the therapeutic benefit of proton pump inhibitors (PPIs) over placebo in patients with laryngopharyngeal reflux (LPR) and to analyze the epidemiological factors of heterogeneity in the literature.

Methods: An electronic literature search was conducted to identify articles published between 1990 and 2018 about clinical trials describing the efficiency of medical treatment(s) on LPR. First, a meta-analysis of placebo randomized controlled trials (RCTs) comparing PPIs versus placebo was conducted according to diet. The heterogeneity, response to PPIs, and evolution of clinical scores were analyzed for aggregate results. Second, a systematic review of diagnosis methods, clinical outcome of treatment, and therapeutic regimens was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

Results: The search identified 1,140 relevant publications, of which 72 studies met the inclusion criteria for a total of 5,781 patients. Ten RCTs were included in the meta-analysis. The combined relative risk was 1.31 in favor of PPIs and increased to 1.42 when patients did not receive diet recommendations. Randomized controlled trials were characterized by a significant heterogeneity due to discrepancies in clinical therapeutic outcomes, diagnosis methods (lack of gold standard diagnostic tools), and therapeutic scheme. The epidemiological analysis of all articles supports the existence of these discrepancies in the entire literature. In particular, many symptoms and signs commonly encountered in LPR are not assessed in the treatment effectiveness. The lack of diagnosis precision and variability of inclusion criteria particularly create bias in all reported and included articles.

Conclusion: This meta-analysis supports a mild superiority of PPIs over placebo and the importance of diet as additional treatment but demonstrates the heterogeneity between studies, limiting the elaboration of clear conclusions. International recommendations are proposed for the development of future trials.

Key Words: Laryngopharyngeal, reflux, laryngitis, outcome, symptoms, treatment.

***Laryngoscope*, 129:1174–1187, 2019**

INTRODUCTION

Laryngopharyngeal reflux (LPR) is an inflammatory condition of the upper aerodigestive tract tissues related to direct and indirect effect of gastric or duodenal content reflux, which induces morphological changes in the upper aerodigestive tract. Laryngopharyngeal reflux may affect approximately 4% to 10% of outpatients visiting ear, nose, and throat (ENT) departments[1,2] and up to 75% of patients with refractory ENT symptoms.[3,4] Laryngopharyngeal reflux is associated with pharyngolaryngeal disorders, profuse media otitis, rhinitis, resistant chronic rhinosinusitis, and many inflammatory disorders of the upper aerodigestive tract.[3–5] The common symptoms encountered in LPR are hoarseness, globus, throat clearing, cough, sore throat, and excessive phlegm.[6,7] The usual laryngeal findings related to LPR are arytenoid and vocal cord erythema, posterior commissure hypertrophy, and arytenoid edema.[6–9] Currently, these signs and symptoms are used to suspect the LPR diagnosis with subsequent testing for gastroesophageal or pharyngeal reflux employing 24-hour pH with or without impedance monitoring.

The main controversy in LPR concerns the lack of gold standard in establishing the LPR diagnosis because

Additional supporting information may be found in the online version of this article.

From the Laryngopharyngeal Reflux Study Group of Young-Otolaryngologists of the International Federations of Oto-rhino-laryngological Societies (YO-IFOS) (J.R.L., S.S., A.S., P.K., A.L.H., B.H., L.G.DM., C.F., F.J.); the Laboratory of Anatomy and Cell Biology, Faculty of Medicine, UMONS Research Institute for Health Sciences and Technology (J.R.L., S.S., L.G.DM., F. J.); the Laboratory of Phonetics, Faculty of Psychology, Research Institute for Language Sciences and Technology, University of Mons (UMons) (J.R.L., B.H.), Mons; the Department of Otorhinolaryngology and Head and Neck Surgery, CHU de Bruxelles, CHU Saint-Pierre, School of Medicine, Université Libre de Bruxelles (S.S.); the Information Management Unit, Institut Jules Bordet, Université Libre de Bruxelles, School of Medicine (M.P.), Brussels; the Department of Otorhinolaryngology and Head and Neck Surgery, CHU de Liège, Faculty of Medicine, University of Liège (C.F.), Liège, Belgium; the Department of Biomedical and Clinical Sciences, Phoniatric Unit, L. Sacco Hospital, University of Milan (A.S.), Milan, Italy; the Department of Otorhinolaryngology and Head and Neck Surgery, Thessaloniki Medical School (P.K.), Thessaloniki, Greece; the Department of Otorhinolaryngology and Head and Neck Surgery, American University of Beirut-Medical Center (A.L.H.), Beirut, Lebanon; and the Division of Gastroenterology, Hepatology, Nutrition, Vanderbilt University Medical Center (M.F.V.), Nashville, Tennessee, U.S.A.

Editor's Note: This Manuscript was accepted for publication on September 10, 2018.

These authors contributed equally to this work.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Send correspondence to Dr. Jerome R. Lechien, MD, PhD, MS, Laboratory of Anatomy and Cell Biology, Faculty of Medicine, University of Mons (UMONS), Avenue du Champ de mars, 6, B-7000 Mons, Belgium. E-mail: jerome.lechien@umons.ac.be

DOI: 10.1002/lary.27591

impedance-pH metry is not perfect (i.e., high false-positive and false-negative rates, interpretation difficulties, placement probe, cost, anatomical differences, limitation of the recording sensors in interrogating the entire cavity the pharynx).[10,11] For this reason, many physicians increasingly consider the clinical response to empirical medical treatment a reliable alternative approach to confirm the diagnosis.[7,12,13] In this approach, only patients unresponsive to empiric therapy undergo ambulatory reflux testing. Treatment efficiency is most commonly evaluated through evolution of signs and symptoms posttherapy. Optimal therapeutic regimen for patients with suspected LPR remains aggressive acid suppressive therapy with proton pump inhibitors (PPIs).[14] Therapeutic response to PPI therapy has been mixed and clinically controversial. This is especially important given the potential association between PPI therapy and the occurrence of chronic adverse affects.[15]

Thus, the primary objective of this study was to investigate the therapeutic benefit of PPI therapy over placebo in patients suspected of having LPR in the context of placebo randomized controlled trials (RCTs). In addition, based on this meta-analysis we propose a list of recommendations for the development of future trials.

MATERIALS AND METHODS

The criteria for considering studies for the systematic review were based on population, intervention, comparison, and outcome framework.

Types of Studies

Double-blind placebo RCTs were initially included to realize the meta-analysis. For the systematic review, we included clinical and observational studies published as full-scale original articles in peer-reviewed journals. The studies should be written in English or French.

Participants

Diagnosis of LPR had to include symptoms ± signs ± objective examination(s). Patients with a positive pH metry or pH-impedance metry were considered as *LPR patients.* Patients with a positive response to empirical therapeutic trial were considered as *highly suspected of LPR* but not as LPR patients.[12,13] Patients included on the basis of LPR symptoms ± signs without known response to PPI therapy were considered as *suspected LPR patients*.

Intervention

The patient may have been treated with diet and lifestyle modifications, medication (i.e., PPIs, alginate, antihistamine, gastroprokinetic), or placebo for at least 4 weeks.

Comparison and Outcomes

Authors may have followed natural history of symptoms with no active treatment or may have not conducted any comparisons.

Search Strategy

A PubMed, Biological Abstracts, BioMed Central, Cochrane, and Scopus search was conducted to identify articles published between January 1990 and March 2018 about clinical trials describing the efficiency of medical treatment(s) on LPR clinical and symptoms. The keywords used were "reflux," "laryngopharyngeal," "laryngitis," "symptom(s)," "gastroeosophageal," "treatment," and "sign(s)." In addition, references were obtained from citations within the retrieved articles or in review publications. Three independent authors (J.R.L., S.S., and L.G.DM.) screened and selected each study that had database abstracts, available full texts, or titles referring to the condition. This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist for reviews and meta-analysis.[16]

Epidemiological Characteristics, Outcomes, and Interventions

Three investigators (J.R.L., S.S., and L.G.DM.) analyzed trials for number of subjects, age, sex, study design, inclusion and exclusion criteria, quality of trial, evidence level (EL), symptoms and signs used as outcome treatment, and treatment types.

Exclusion criteria adopted in trials were extracted and were classified in seven categories (cat.): cat. 1, authors carefully excluded patients with ENT and respiratory toxic or infectious disorder(s) within the last month; cat. 2, smoker, alcoholic, and subjects with active allergy; cat. 3, patients with anti-reflux treatment already started in the previous month (i.e., PPIs, H_2 receptor antagonists, over-the-counter antacids, gastroprokinetic, and surgery); cat. 4, patients with current/history of malignancies, radiotherapy, laryngeal trauma, and head and neck previous surgery; cat. 5, benign laryngeal lesions including cyst, nodules, polyps, and papillomatosis; cat. 6, severe neurologic and psychiatric disorders (i.e., severe depression, dementia, psychosis); and cat.7, subjects with other ENT diseases that may lead to confounding ENT complaints.

The three investigators performed the extraction of symptoms and signs used as therapeutic outcomes. For this purpose, to be included the studies had to precisely describe symptoms and/or signs assessed throughout the treatment course. Therefore, symptom and sign outcomes could consist of clinical questionnaires or simply history/observation taken by the clinician. In cases of discrepancies between investigator's results, a second analysis of the content of the publication was made.

Validity Evaluation, Tools, and Risk of Bias

The grade of recommendation was determined for each publication.[17] Risk of bias was assessed using the Tool to Assess Risk of Bias in Cohort Studies (TARB) developed by the Clarity Group and Evidence Partners and included an analysis of selection, detection, performance, attrition, and reporting biases.[18]

Statistical Analysis

Data were analyzed for aggregate results for two endpoints: the response to PPIs (as binary endpoint) and the evolution of the scores assessed for signs and symptoms (as continuous outcome). Analyses were focused on placebo RCTs employing PPI therapy.

For response to PPI, we calculated individual relative risks for PPI effect (when the numbers of responders as well as

15314995, 2019, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/lary.27591 by Thirion Paul - Dge, Wiley Online Library on [29/01/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

numbers of randomized patients were available per arm), and we aggregated them first with a fixed effect method (Peto method). That is, we we applied the formulas provided by Cucherat et al.[19] to calculate: the individual relative risks, the logarithms of those relative risks, and their variances. The inverses of the variances were used as weights to calculate the logarithm of the aggregated relative risk and its variance. Finally, the estimate of the aggregated risk was obtained together with a 95% confidence interval (CI), assuming a normal distribution on the logarithmic scale. A test statistic following a chi square distribution was obtained from the individual weights and individual logarithms of the relative risks.

In cases of heterogeneity detected using a chi square test for heterogeneity, we also applied a random effects model. This means that the weights used to aggregate the individual relative risks on the logarithmic scales were modified to integrate the measure of the heterogeneity between studies according to the formulas of Cucherat et al.[19]

We planned a subgroup's analysis according to the fact that patients had diet as complementary treatment or not. We considered the aggregated relative risk as showing statistically significant effect if the 95% CI for the aggregated relative risk did not overlap with 1. For scores, we defined as continuous measure in each treatment arm the score differences before and after treatment. We calculated a standardized treatment effect per trial, and we also calculated an aggregated standardized treatment effect using a weighted mean of individual treatment effects as for the response to PPI (as binary endpoint). The same steps were followed, adapting the formulas to these individual estimates of the treatment effects (all the formulas available in Cucherat et al.[19]). All analyses were performed using a modified version of Microsoft Excel 2016 (Microsoft Corp., Redmond, WA).

Overview of Clinical and Epidemiological Characteristics in the Entire Literature

In addition to the meta-analysis (i.e., combined relative risk and heterogeneity), we extended our epidemiological analysis to all trials conducted during the 3 past decades with the aim to assess the clinical efficiency of LPR treatment(s). Thus, in a second step, the three investigators performed the same extraction and analysis of data (i.e., patients age, sex, diagnosis method, exclusion criteria, outcomes used, and treatment types) for all controlled or uncontrolled, prospective or retrospective studies conducted within the 3 past decades. The intent of this analysis was to allow robust overview of trials characteristics of the current literature in LPR, which may allow the elaboration of recommendations for future trials.

RESULTS

We identified 1,140 relevant publications from 72 pertinent references accounting for 5,781 suspected or confirmed LPR patients. Of the 72 qualified articles, we found 15 placebo RCTs, 13 prospective controlled trials (with or without randomization), 40 prospective uncontrolled studies, and four retrospective case series (Supporting Supporting information Table 1).[2,3,7,11,13,20–85] The ELs are described in Figure 1. Seven studies were excluded due to overlapping patient populations.[78,87–92]

Two placebo RCTs included in previous meta-analysis[93] were excluded because focusing on patients with chronic cough attributed a posteriori to LPR.[94,95] The degree of agreement between investigators was high because only three articles have been discussed about the inclusion.

Meta-Analysis Results

Among the 15 placebo RCTs, two trials were excluded from the analysis because the treatment was only based on alginate[29,33]; one study was excluded due to use of voice therapy in addition to PPIs.[28] Two studies were considered as inadmissible due to insufficient information in the publications (i.e., percentage of patients who had > 50% of symptoms improvement).[30,31] Thus, our analysis concerned a total of 10 placebo RCTs, accounting for 480 patients (220 in the placebo arms and 260 in the PPI arms; not all trials used a 1:1 allocation ratio).[11,20–27,32]

Employing a fixed effects model, we obtained a combined relative risk of 1.26 (95% CI: 1.07–1.46) in favor of PPIs. However, significant heterogeneity was detected (chi square = 15.65; 9 degrees of freedom, $P = 0.05$). Using a random effects model, combined relative risk increased to 1.31 with a broader 95% CI (1.03–1.67), but statistical significance was maintained in favor of PPIs. The relative risks of placebo RCTs are described in Figure 2.

Subgroups analysis assessed role of diet in three studies (74 patients in the placebo arms and 70 patients in the PPI arms). Combined relative risk with Peto method was 1.27, 95% CI (1.01–1.59), without detecting any significant heterogeneity. On the other hand, looking at the seven studies with PPIs but without systematic diet proposed to the patients (respectively 146 patients for placebo and 190 patients for PPI), we had to use a random effects model and got a nonsignificant result with a combined relative risk of 1.42, 95% CI from 0.96 to 2.09 (Fig. 2). In the subgroup analysis, additional data regarding dietary implementation were gathered post hoc by contacting the primary investigators if such data were not detailed in the article.

Laryngopharyngeal Reflux Patient Characteristics, Diagnosis, and Treatments. Among the 10 placebo RCTs, we identified seven diagnosis methods, 10 lists of exclusion criteria, 10 combinations of clinical outcomes used throughout treatment, nine therapeutic regimens, and three treatment durations. Moreover, some authors combined the intake of a placebo with diet and behavioral changes,[20,24,32] whereas other did not prescribe diet.[11,21–23,25–27]

Clinical Outcomes as Treatment Effectiveness. Among the 10 placebo RCTs included in our meta-analysis, there was significant heterogeneity across studies about clinical therapeutic outcomes because a total of 10 different combinations of symptoms and signs were employed to determine the PPIs/placebo effectiveness. In addition, only a small number of placebo RCTs provided information about the evolution of individual symptoms or signs throughout the treatment.[11,24,27] Only four[25–27,32] authors used standardized tools to assess signs (Reflux Finding Score [RFS] and chronic posterior laryngitis

15314995, 2019, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/lary.27591 by Thirion Paul - Dge, Wiley Online Library on [29/01/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

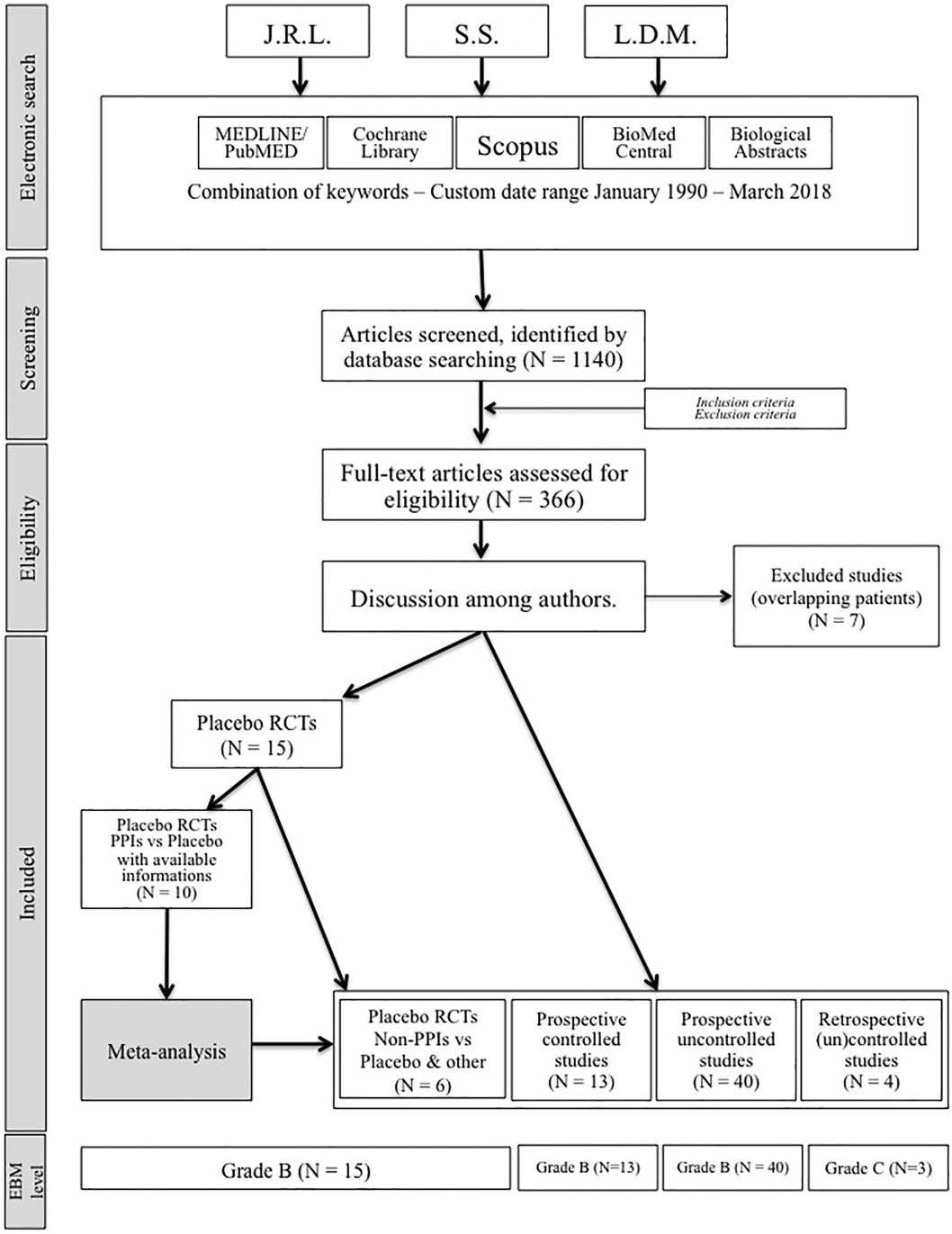

Fig. 1. Flow chart shows the process of article selection for this study.
RCT = randomized controlled trials; EBM = evidence-based medicine; JRL = Jerome R. Lechien; LDM = Lisa G. De Marrez.

index) and symptoms (Reflux Symptom Index [RSI]) throughout treatment. No authors performed blinded assessment of laryngo(strobo)scopic signs with regard to the symptoms of patients.

Overview of Clinical and Epidemiological Characteristics in the Entire Literature

Epidemiological Characteristics of Studies. To investigate the heterogeneity factors in the current literature, we extended the epidemiological analysis to all prospective and retrospective studies (N = 72). Supporting information Table 1 summarizes the 72 studies, which are classified according to their ELs.[2,3,7,11,13,20–86] The sample sizes ranged from 10 to 1,044 subjects. Fifty-seven percent of patients were women, and the average patient age at diagnosis was 48.9 years old. There was an important heterogeneity among studies regarding the diagnosis method. The diagnosis was based on the evaluation of symptoms and signs without standardized tool in

15314995, 2019, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/lary.27591 by Thirion Paul - Dge, Wiley Online Library on [29/01/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Authors	Year	Placebo (N)	PPIs (N)	Pl response	PPIs response	Diet & BC	RR
Havas	1999	8	7	5	7	+	1.60
El-Serag	2001	10	10	1	6	-	6.00
Noordzij	2001	15	15	6	9	-	1.50
Langevin	2001	16	14	3	11	-	4.19
Eherer	2003	7	7	6	6	-	1.00
Steward	2004	21	21	9	8	+	0.89
Vaezi	2006	50	95	23	40	-	0.92
Wo	2006	20	19	8	8	-	1.05
Reichel	2008	28	30	11	22	-	1.87
Ezzat	2011	45	42	29	34	+	1.26

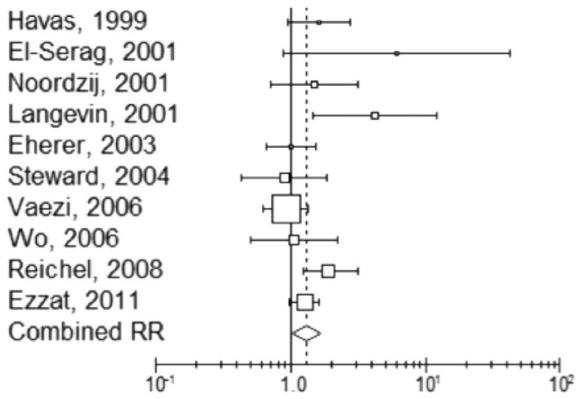

Fig. 2. Meta-analysis results of placebo randomized controlled trials included in the meta-analysis.
PPI = proton pump inhibitors; RCT = randomized controlled trials; PI = pantoprazole/proton pump Inhibitor; RR = relative risk; BC = behavioral changes.

the majority of publications, followed by the pH-impedance monitoring and utilization of RSI and RFS scores with many validated and unvalidated thresholds (Table I). Among the trials using pH-impedance studies, the criteria used to perform the diagnosis were inaccurate[75,86] or significantly different across studies (Table II). Thus, a few authors consider the occurrence of a/multiple pharyngolaryngeal drop(s) with a pH below 4 or 5[11,51,56] for the diagnosis, whereas others used composite criteria involving the use of Ryan score or other.[26,43,84–86] In trials that based the diagnosis on both signs and symptoms, more than 40% of the included studies did not provide information about the exclusion criterias[37,39,45–50,52,53,55–58,62,75,76,85,86] or did not exclude some major cofounding factors such as smoking or alcoholism, representing a selection bias according to our analysis with TARB.[3,21,31,33,40–42,50,59,72,82,83] Overall, four main different medical regimens were identified with a duration ranging from 4 to 54 weeks:

1. PPIs alone once a day (N = 18), twice a day (N = 45), or three times a day (N = 2);
2. PPIs in association with other drugs including gastroprokinetic (N = 5), H_2 receptor antagonists (N = 1), rikkunshito (N = 1);
3. PPIs combined with speech therapy (N = 2);
4. Other drugs or diet or placebo alone (especially in controlled studies, N = 6).

Clinical Outcomes of Open Labelled Studies. In more than 50% of included studies, symptoms were mainly evaluated along the treatment with unstandardized composite questionnaires (Supporting information Table 1). Authors usually excluded patients who did not complete the therapeutic course, reducing the risk of attrition bias. The evaluation of videolaryngo(strobo)scopic signs was mainly performed with RFS, followed by unstandardized composite instrument or without instrument/score. Only a few authors used a blinded assessment for the videolaryngo(strobo)scopic signs.[7,54,59,63] The precise symptoms and signs used to assess the medical treatment effectiveness are described in Table III. As described in Table IV, at the moment of evaluation of the signs the vast majority of authors were not blinded to patient clinical improvement or cure, representing a detection bias according to our analysis with TARB. Overall, signs and symptoms described in RFS and RSI were the most commonly assessed clinical outcomes throughout therapeutic course. Some usual laryngeal and extralaryngopharyngeal signs related to LPR disease were not often described in the current literature (Fig. 3). In addition, as found in placebo RCTs, a few studies provided information about the evolution of individual symptoms or signs throughout the treatment.[7,28,30,31,52,60]

Table IV (supplementary file) provides bias analysis of included studies according to TARB. This table exhibits the high heterogeneity between studies according to

15314995, 2019, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/lary.27591 by Thirion Paul - Dge, Wiley Online Library on [29/01/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE I.
Diagnosis Methods and Tools Used in the Selected Studies

Diagnosis Method	N studies
LPR symptoms and signs (no tool)	34
Symptoms since at least 3–4 weeks	4
Symptoms since at least 6–8 weeks	2
Symptoms since at least 12–14 weeks	6
Symptoms duration not provided	22
Empirical PPIs scheme	1
LPR Symptoms (no tool)	15
Symptoms since at least 3–4 weeks	2
Symptoms since at least 6–8 weeks	2
Symptoms since at least 12–14 weeks	3
Symptoms duration not provided	8
Tools and Thresholds	
RSI > 13 and RFS > 7	11
RSI > 13	4
RSI > 10 and RFS > 5	2
RSI > 9 and RFS > 7	1
RSI ≥ 13	1
RSI > 13 and signs	1
RFS > 7 and symptoms	2
CPLI and symptoms	1
GSRS ≥ 3	1
pH (impedance) metry	18
Esophagitis	7

CPLI = Chronic Posterior Laryngitis Index; GSRSI = Gastrointestinal Symptom Rating Scale; LPR = laryngopharyngeal reflux; m = months; N = number; PPI = proton pump inhibitors; RFS = reflux finding score; RSI = reflux symptom index.

diagnosis, exclusion criteria, outcomes evaluations, and treatment regimens. In the large majority of studies, the risk of bias was high.

DISCUSSION

Our meta-analysis highlights two main findings: On the one hand, our relative risk analysis supports a modest superiority of PPIs over placebo but exhibits a significant heterogeneity between studies. On the other hand, the relative risk of trials, including diet and behavioral changes in both PPIs and placebo arms, is lower than the relative risk of trials that compared PPIs versus placebo without diet and behavioral changes.

Demonstration of the superiority of PPIs over placebo does not corroborate the results of the most recently published meta-analysis of Guo et al.[93] Many reasons explain this inconsistency. First, the trials included in our two meta-analyses differ significantly. Because the quality of placebo RCTs included in a meta-analysis had a dramatic impact of the results of the meta-analysis, we decided to adopt strict inclusion criteria. Thus, in the present study we only included placebo RCTs focused on the efficiency of PPIs over placebo in the context of LPR disease. In the study of Guo et al., authors included one controlled study comparing diet versus PPIs (without placebo arm)[42] and two trials that studied patients with chronic cough[94,95] without clinical or objective demonstration of LPR. Moreover, two placebo RCTs were excluded from our analysis with regard to the lack of required information for our statistical analysis. Thus, our study is more rigorous in its inclusion criteria. However, we did find significant heterogeneity between placebo RCTs due to discrepancies regarding diagnosis methods, clinical therapeutic outcome, and treatment regimens. Indeed, these three elements traditionally constitute the main causes of heterogeneity between placebo RCTs, impacting the meta-analysis results.[96] Our second finding suggests that diet and behavioral changes is a factor that modulates the therapeutic effectiveness of PPIs and placebo. This point is particularly important because the consideration of diet and behavioral changes as a treatment of LPR has already been supported[68] in many trials but still not really taken into account.

We also performed an in-depth assessment of all prospective and retrospective studies in the area of LPR from 1990 to 2018, covering a period of 28 years. This was performed to better determine the heterogeneity of current data in order to guide recommendations for future trials. In doing so, we confirmed the presence of substantial heterogeneity between studies regarding diagnosis criteria with a large number of studies that did not use pH-impedance monitoring or validated clinical instruments. From an epidemiological standpoint, inclusion or exclusion criteria in a specific study population have a dramatic impact on the conclusions of the treatment effectiveness.[97] Therefore, in trials that did not use objective examinations for the diagnosis, the utilization of the empirical approach must carefully involve clear selection of the patients excluding all possible differential diagnoses.[97,98] In practice, many authors using empirical approach did not exclude the main confounding factors or did not provide information about the exclusion criteria, which lead to mis-selection of LPR patients and selection bias. The most blatant example concerns the chronic consumption of alcohol or smoking, which are known to be associated with many symptoms and signs of chronic pharyngolaryngitis. Additionally, others excluded patients with signs that may be related to LPR including laryngeal granuloma,[51] tongue tonsil hypertrophy,[75] or severe esophagitis,[20] introducing a selection bias according to the profile of the selected patients. With further regard to the diagnosis, the criteria used to perform the diagnosis with pH-impedance monitoring were unclear[75,86] or significantly varied among studies that underlies different patient's profiles according to the severity of LPR and a potential selection/recruitment bias. Along this line, our analysis identified a total of 11 different criteria for 17 studies using pH-(impedance) monitoring with overall good homogeneity in the probes' placement.

To improve patient care, it is recommended to use reliable and effective tools in assessing LPR symptoms and signs both at the diagnosis and throughout the treatment. One of the main findings highlighted by our analysis is the full widespread utilization of RSI and RFS, which undoubtedly improves patient care but may underlie an implicit bias related to the exclusion of some

15314995, 2019, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/lary.27591 by Thirion Paul - Dge, Wiley Online Library on [29/01/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE II.
Overview of the pH Metry Criteria Used for the LPR Diagnosis

References	pH Metry Type	Diagnosis Criterias	Probe(s) Placement
Noordzij, 2002	Dual-probe pH metry	Drop in pH ≤ 4, or 3-point drop in pH < 5	Proximal probe: hypopharynx, 1 cm above UES Distal probe: esophagus, 18 cm below the upper probe
Belafsky, 2001 & 2002	Dual-probe pH metry	Drop in pH ≤ 4 both in Oropharyngeal and esophageal spaces	Proximal probe: hypopharynx, 1 cm above UES
DelGaudio, 2003	Dual-probe pH metry	Drop in pH ≤ 4 in oropharyngeal space	Proximal probe: hypopharynx, 1 cm above UES
Eherer, 2003	Dual-probe pH metry	Distal probe: pH ≤ 4 (4.5% time)	Distal probe: esophagus, 18 cm below the upper probe Proximal probe: hypopharynx, 1–3 cm above UES
Steward, 2004	Dual-probe pH metry	Distal probe: pH ≤ 4 (4.5% time)	Distal probe: esophagus, 5 cm above LES Proximal probe: unspecified area, 15 cm proximal to LES
Qaader, 2005	Simple-probe pH metry	NA	Distal probe: esophagus, 5 cm above LES NA
Wo, 2006	Triple-probe pH metry	A drop in pH ≤ 4.0 for ≥ 5s and Onset of abrupt pH drop to nadir in < 30s and pH drop with distal pH sensor pH < 4.0 and Proximal sensor pH > distal sensor pH	Proximal probe: hypopharynx, 1–3 cm above UES Distal probe: esophagus, 5 cm above LES
Swoger, 2006	Dual-probe pH metry	Distal probe: pH ≤ 4 (5.5% time)	Proximal probe: hypoharynx, below UES
Reichel, 2008	Dual-probe pH metry	Drop in pH ≤ 4 both in oropharyngeal and Esophageal spaces with RAI > 6.3	Distal probe: esophagus, 5 cm above LES Proximal probe: hypopharynx, above UES
Jin, 2008	Dual-probe pH metry	Drop in pH ≤ 4 both in Oropharyngeal and esophageal spaces	Distal probe: 15 cm below the upper probe Proximal probe: hypopharynx, above UES
Koufman, 2011	Dual-probe pH metry	NA	Distal probe: 15 cm below the upper probe NA
Friedman, 2011	Pharyngeal probe pH metry Restech	Ryan score > 9.41 (upright) or Ryan score > 6.8 (supine)	Probe: hypopharynx, above UES
Lien, 2013	Triple-probe pH metry	≥ 2 LPR pharyngeal episodes or Excessive distal esophageal acid reflux	Proximal probe: hypopharynx, 1 cm above UES Distal probe: esophagus, 5cm above LES
Waxman, 2014	Pharyngeal probe pH metry (Restech)	Ryan score > 9.4 (upright) or Ryan score > 6.8 (supine position)	NA
Wan, 2014	Dual-probe pH/impedance Metry	≥ 3 LPR pharyngeal episodes or Proximal acid exposure time >1%, or Impedance proximal acid exposure ≥ 4	Proximal probe: esophagus, 2 cm below UES Distal probe: 20 cm below the proximal probe
Nennstiel, 2016	Dual-probe pH/impedance Metry	Distal probe: pH ≤ 4 (4.0% time) Impedance: > 73 fluids/22 hours or Esophageal mixed reflux episodes	Proximal probe: NA Distal probe: esophagus, 5 cm above LES
Tseng, 2018	6-probe pH/impedance Metry	Distal probe: pH ≤ 4 (4% time)	Proximal probe: NA Distal probe: esophagus, 3 cm above LES

LES = lower esophageal sphincter; NA = not available; RAI = reflux area index; UES = upper esophageal sphincter.

common symptoms and signs that are not described in these instruments. Thus, throat pain,[14] odynophagia,[11] or halitosis[99] are commonly met in patients with LPR but still not described in RSI. Other symptoms such as heartburn, chest pain, regurgitations, and indigestion are described within a single combined item, leading to confusion in the assessment of these complaints. In addition, the popularity of LPR as a causative factor for ear complaints (ear pressure, pain) has increased steadily over the past 3 decades[100,101] but is still not take into consideration in any patient-reported instrument. Another problem related to RSI is the rating of symptoms that is only based on the symptom's severity. The rating of symptom's severity with visual analog scale remains subjective and depends on many sociocultural factors. Thus, two patients with same symptoms could differently rate the symptom's severity, impacting the RSI total score, which is used for patient's inclusion (RSI > 13) and the assessment of post-therapeutic response. It is partly for this subjective aspect that a few authors prefer to assess both frequency and intensity of each symptom with a clear definition of the corresponding rates.[60,86] With regard to signs assessment, vocal fold erythema, keratosis, and a large number of extralaryngeal signs (i.e., posterior pharyngeal wall inflammation, anterior pillars inflammation, coated tongue) are not evaluated with RFS, although they concern a considerable number of patients.[45,102,103] Moreover, some usual signs related to LPR (i.e., leukoplakia, granuloma)[102] consisted of exclusion criteria in other studies.[51] In addition, our analysis suggests that only a few authors performed blinded evaluations with regard to the patient complaints.[7,59,104] As previously demonstrated, the unblinded assessment of laryngoscopic signs is associated with a high risk of sign's misestimation because physician judgment is strongly influenced by knowledge of patient complains.[105,106] Naturally, a blinded examination is difficult in daily practice, which is why it is important to have signs scores with precise descriptions of each signs items grade exhibiting higher interjudge reliability. All weaknesses related to the current LPR instruments may

15314995, 2019, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/lary.27591 by Thirion Paul - Dge, Wiley Online Library on [29/01/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE III.
Symptoms and Signs Outcomes Used in the Selected Studies

Symptoms Number of Studies N = 69			Signs Number of Studies N = 55		
Laryngopharyngeal			Laryngopharyngeal		
Voice disorders	VD	66	Laryngeal/arytenoids erythema	EH	52
Throat clearing	TC	65	Granuloma/granulation (interarytenoid nodularity)	GG	51
Troublesome cough	CT	63	Laryngeal edema	LE	49
Globus sensation	GS	62	Posterior commissure hypertrophy	PH	45
Dysphagia	DD	52	Vocal fold edema	VE	44
Stomach acid coming up	PS	48	Thick endolaryngeal mucous	TM	38
Excess throat mucous/postnasal drip	EM	41	Subglottic edema/pseudosulcus/stenosis	SE	37
Coughing after you ate/lying down	PC	40	Ventricular obliteration	VV	35
Chest pain	CP	39	Vocal fold erythema	VR	14
Chocking	CK	34	Laryngeal ulcerations	UC	10
Sore throat/throat pain	PT	25	Supraglottis erythema	SR	8
Odynophagia	OD	9	Posterior pharyngeal wall erythema	PW	7
Tongue burning	TB	3	Supraglottis edema	SP	7
Ear pressure/pain	EP	2	Polyp/Reinke edema	PP	5
Wheezing	WH	1	Postpharyngeal cobblestoning	PY	5
			Subglottic erythema	SU	3
Gastroesophageal			Loss light reflect	LO	2
Heartburn	HB	61	Nodules	ND	2
Regurgitations	RE	19	Leukoplakia	LL	2
Abdominal pain	AP	3	Vocal cord epithelium thickening	TI	1
Diarrhea syndrome	DS	3	Vocal web	WW	1
Indigestion	IS	3	Laryngeal keratosis	KT	1
Nausea	NA	3	Mucous pooling in the piriform sinus	PI	1
Eructation	EE	3			
Hiccup	HO	1	Extra laryngopharyngeal		
Constipation	CS	1	Tongue tonsil hypertrophy	TT	5
Foul taste	FT	1	Posterior oropharyngeal wall erythema	PO	2
			Nasal congestion	NC	1
			Uvula erythema/edema	UV	1
			Anterior pillars erythema/edema	AN	1
			Dull tympanic membrane	DT	1

AN = anterior pillar erythema/edema; AP = abdominal pain; CK = chocking; CP = chest pain; CS = constipation; CT = troublesome cough; DD = dysphagia; DS = diarrhea syndrome; DT = dull tympanic membrane; EE = eructation; EH = laryngeal/arytenoids erythema; EM = excess throat mucous/postnasal drip; EP = ear pressure/pain; F = frequency; FT = foul taste; GG = granuloma/granulations (posterior commissure); GS = globus sensation; HB = heartburn; HO = hiccup; IS = indigestion; KT = laryngeal keratosis; LE = laryngeal edema; LL = leukoplakia; LO = loss light reflect; m = month(s); NA = nausea; NC = nasal congestion; ND = nodules; OD = odynophagia; PC = Coughing after you ate/lying down; PH = posterior commissure hypertrophy; PI = mucous pooling in the piriform sinus; PO = posterior oropharyngeal wall erythema; PP = polyposis/Reinke edema; PS = stomach acid coming up; PT = pain throat; PW = posterior pharyngeal wall erythema; PY = postpharyngeal cobblestoning; RE = regurgitations; S = severity; SA = stomachache; SE = subglottic edema; SP = supraglottis edema; SR = supraglottis erythema; TB = tongue burning; TC = throat clearing; TI = vocal cord epithelium thickening; TM = thick endolaryngeal mucous; TT = tongue tonsil hypertrophy; UC = laryngeal ulcerations; UV = uvula erythema/edema; VD = voice disorders; VE = vocal folds edema; VR = vocal folds erythema; VV = ventricular obliteration; w = week(s); WH = wheezing; WW = vocal web.

undoubtedly decrease the reliability and efficiency of clinical evaluations at baseline and throughout the treatment, leading to controversial conclusions between studies.[14]

The impact of gastroduodenal refluxate on the laryngopharyngeal sensitivity is another point that needs clarification. Laryngopharyngeal sensitivity is important to protect the airway of microaspirations. Indeed, physiologically, the stimulation of the laryngeal mucosa with irritative molecules (such as pepsin or trypsin) induces a pharyngeal swallow reflex and cough.[107] Some studies suggested that the laryngeal inflammation related to LPR is associated with a decrease of the laryngopharyngeal sensitivity that potentially increases the risk of microaspirations of gastroduodenal refluxate.[108,109] According to the fact that recurrent microaspirations is one of the potential mechanisms explaining chronic cough, throat clearing, and an increased susceptibility to respiratory diseases,[110,111] future additional examinations could be developed to better assess the mucosa sensitivity, especially in patients with LPR and respiratory-related disease.

Dietary therapy could be important because it is associated with significant improvement of signs and symptoms in both responder and nonresponders patients

15314995, 2019, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/lary.27591 by Thirion Paul - Dge, Wiley Online Library on [29/01/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE IV.
(supplementary table): Risk of bias assessment according to studies

References	LPR diagnosis	Exclusion criteria	Outcomes definition	Symptoms - Assessment	Adequate finding assessment	Blinded Assessment (findings)	Adequate follow-up duration
Havas (20)	Probably yes	No	Yes	Probably no	N.A.	N.A.	Yes
El-Serag (21)	Probably yes	Probably no	Yes	Probably yes	Probably yes	No	Yes
Noordzij (11)	Yes	Yes	Yes	Probably yes	Probably yes	No	Yes
Langevin (22)	Probably yes	Probably yes	Yes	Probably no	N.A.	N.A.	Yes
Eherer (23)	Yes	Probably yes	Yes	Probably yes	Probably yes	No	Yes
Steward (24)	Probably yes	Yes	Yes	Yes	Probably no	No	Yes
Vaezi (25)	Probably yes	Yes	Yes	Probably yes	Probably yes	No	Yes
Wo (26)	Yes	Probably no	Yes	Probably yes	Probably yes	No	Yes
Reichel (27)	Probably yes	Yes	Yes	Probably yes	Probably yes	No	Yes
Vashani (28)	Probably yes	Probably yes	Yes	Probably yes	Yes	No	Probably yes
McGlashan (29)	Probably yes	Probably yes	Yes	Probably yes	Probably yes	No	Yes
Fass (30)	Probably yes	Probably no	Yes	Probably yes	Probably yes	No	Yes
Lam (31)	Probably yes	Yes	Yes	Probably yes	Probably yes	No	Yes
Ezzat (32)	Probably yes	Yes	Yes	Yes	Probably yes	No	Yes
Tseng (33)	Yes	Probably yes	Yes	Probably yes	Probably yes	No	Yes
Siupsinkiene (34)	Probably yes	Probably yes	Yes	Probably no	Probably no	No	No
Park (35)	Probably yes	Probably no	Yes	Probably yes	N.A.	N.A.	Yes
Swoger (36)	Yes	Probably no	Yes	Probably yes	Yes	No	Yes
Hunchaisri (37)	Probably yes	No	Yes	Probably yes	N.A.	N.A.	Yes
Chung (38)	Probably yes	Probably yes	Yes	Probably yes	Probably yes	No	Yes
Oridate (39)	Probably yes	No	Probably yes	N.A.	Probably yes	No	Probably no
Chun (40)	Probably yes	Probably no	Yes	Probably yes	Probably yes	No	Yes
Tokashiki (41)	Probably yes	Probably no	Yes	Probably yes	N.A.	N.A.	Probably no
Chappity (42)	Yes	Probably no	Yes	Yes	Probably no	No	Yes
Wan (43)	Yes	Yes	Yes	Probably yes	Probably yes	No	Probably no
Ozturan (44)	Probably yes	Probably yes	Yes	Probably yes	Probably yes	No	Yes
Hanson (45)	Probably yes	No	Yes	Probably no	Probably yes	No	Probably no
Jaspersen (46)	Probably yes	No	Yes	Probably no	N.A.	N.A.	Probably no
Shaw (47)	Probably yes	No	Yes	Probably yes	Probably no	No	Yes
Wo (48)	Probably yes	No	Yes	Probably yes	N.A.	N.A.	Yes
Metz (49)	Probably yes	No	Yes	Probably yes	N.A.	N.A.	Probably no
Habermann (50)	Probably yes	No	Yes	Probably yes	Probably yes	No	Probably yes
Belfasky (51)	Yes	Probably yes	Yes	Probably yes	Probably yes	No	Yes
Hamdan (52)	Probably yes	No	Yes	Probably no	N.A.	N.A.	Probably no
Rodriguez (53)	Probably yes	No	Yes	Probably no	Probably no	No	Yes
Habermann (54)	Probably yes	Probably yes	Yes	Probably no	Yes	No	Probably yes
Belafsky (55)	Yes	No	Yes	Probably yes	N.A.	N.A.	Yes
DelGaudio (56)	Probably yes	No	Yes	Probably yes	Probably yes	No	Yes
Bilgen (57)	Probably yes	No	Yes	Probably yes	Probably yes	No	Yes
Garrigues (58)	Probably yes	No	Yes	Probably yes	Probably yes	No	Yes
Beaver (59)	Probably yes	No	Yes	N.A.	Probably yes	Yes	Probably yes
Williams (60)	Probably yes	Yes	Probably yes	Probably yes	Probably yes	No	Yes
Issing (61)	Probably yes	Probably no	Yes	Probably no	N.A.	N.A.	Yes
Sereg-Bahar (62)	Probably yes	No	Yes	N.A.	Probably yes	No	Yes
Qaader (63)	Yes	Probably no	Yes	Yes	Probably yes	No	Yes
Dore (64)	Probably yes	Probably no	Yes	Probably yes	N.A.	N.A.	Yes
Qua (65)	Probably yes	Yes	Yes	Probably yes	Probably no	No	Yes
Jin (2)	Yes	Probably no	Yes	Probably yes	Probably yes	No	Yes
Oridate (66)	Probably yes	No	Yes	Probably yes	N.A.	N.A.	Yes

(Continues)

15314995, 2019, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/lary.27591 by Thirion Paul - Dge, Wiley Online Library on [29/01/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE IV.
Continued

References	LPR diagnosis	Exclusion criteria	Outcomes definition	Symptoms - Assessment	Adequate finding assessment	Blinded Assessment (findings)	Adequate follow-up duration
Chiba (67)	Probably yes	Probably no	Yes	Probably no	N.A.	N.A.	Yes
Koufman (68)	Yes	Probably yes	Yes	Probably yes	Probably yes	No	No
Lee (3)	Probably yes	Probably no	Yes	Probably yes	Probably yes	No	Yes
Masaany (69)	Probably yes	Probably yes	Yes	Probably yes	Probably yes	No	Yes
Naiboglu (70)	Probably yes	Probably yes	Yes	Probably yes	Probably yes	No	Yes
Patigaroo (71)	Probably yes	Probably no	Yes	Probably yes	Probably yes	No	Yes
Habermann (72)	Probably yes	Probably no	Yes	Probably yes	Probably yes	No	Yes
Park (73)	Probably yes	Probably yes	Yes	Probably yes	Probably yes	No	Yes
Becker (74)	Probably yes	Probably no	Yes	Probably yes	N.A.	N.A.	Yes
Lien (75)	Yes	Probably yes	Yes	Probably yes	N.A.	N.A.	Yes
Beech (76)	Probably yes	No	Yes	Probably yes	N.A.	N.A.	Yes
Vailati (77)	Probably yes	Probably no	Yes	Probably yes	Probably yes	No	Yes
Lee (78)	Probably yes	Probably yes	Yes	Probably yes	Probably yes	No	Yes
Semmanaselvan (79)	Probably yes	Probably yes	Yes	Probably yes	Probably yes	No	Yes
Batioglu (80)	Probably yes	Probably no	Yes	Probably yes	Probably yes	No	Yes
Dulery (81)	Probably yes	Probably no	Yes	Probably no	Probably yes	No	Yes
Joshi (82)	Probably yes	Probably no	Yes	Probably yes	Probably yes	No	Yes
Pullarat (83)	Probably yes	Yes	Yes	Probably yes	Probably yes	No	Yes
Lechien 75)	Probably yes	Yes	Yes	Probably yes	Probably yes	Yes	Yes
Friedman (84)	Yes	Probably no	Yes	Probably yes	N.A.	N.A.	Yes
Waxman (85)	Probably yes	No	Yes	Probably yes	N.A.	N.A.	Probably no
Gupta (11)	Probably yes	Probably yes	Yes	Probably yes	Probably yes	No	Yes
Niennstiel (86)	Yes	No	Yes	Probably yes	N.A.	N.A.	Yes

Footnotes: Analysis of LPR diagnosis, exclusion criteria, outcomes definition, and blinded assessment of findings was conducted according to our criteria described in material and methods and the Tool to Assess the Risk of Bias in Cohort Studies developed by the Clarity Group and Evidence Partners. The assessment of the finding assessment included i) the use of adequate instrument (i.e. stroboscopy in the evaluation of vocal fold motion or fibroscopy in the evaluation of upper aerodigestive tract mucosa), ii) the relevance of findings (i.e. evaluations of laryngeal, pharyngeal, and oral mucosa), and iii) the characteristics of the assessor. According to previous studies,[2] we considered a treatment of ≥8 weeks as appropriate.

to PPIs.[7,68] By going further in terms of cost-effective approach, the use of diet and behavioral changes in mild LPR disease could be explored to reduce the cost related to the PPIs overconsumption. Moreover, surprisingly, no placebo RCTs assessed the combination of PPIs and alginate-based formulations (or magaldrate), although that can be a useful treatment for mixed (acid and nonacid) LPR. However, nonacid reflux is less explored in LPR disease. Another difference among the therapeutic schemes is duration of the empiric trial. The improvement of both signs and symptoms may take time, especially in patients with a long history of LPR.[112,113] To date, most researches support a period of 2 to 6 months of treatment to get substantial therapeutic benefit.[14,114,115] Thus, the short therapeutic period of some trials may also impact the evaluation of treatment effectiveness.[39,41,45,46,49,52,68,79,85] This is especially the case for some signs requiring more time to improve, such as posterior commissure hypertrophy.[7] This point enhances the interest to conduct global and individual symptoms and signs evolution throughout treatment analyses. Based on the epidemiological analysis of this study, the LPR Study Group of Young-Otolaryngologists of the International Federation of Oto-rhino-laryngological Societies proposed some valuable recommendations for the future clinical studies interested in the impact of the medical treatment on both LPR symptoms and signs (Table V). Moreover, our group is currently working to develop a new symptom tool: the Reflux Symptom Score (Fig. 4).

The main limitations of this meta-analysis concern the low number of studies that meet our inclusion criteria, the small sample sizes of included trials, and the various biases developed in our discussion. The combination of these conditions probably impacts the results of our meta-analysis.

CONCLUSION

This meta-analysis supports a moderate superiority of PPIs over placebo and the importance of diet as additional treatment. However, we identified an important heterogeneity between studies limiting the elaboration of a clear conclusion in a large number of placebo-RCTs. In this context, the systematic use of PPIs in the LPR treatment should be balanced with the potential side effects of these drugs and their interaction with other medications. Therefore, future

15314995, 2019, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/lary.27591 by Thirion Paul - Dge, Wiley Online Library on [29/01/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

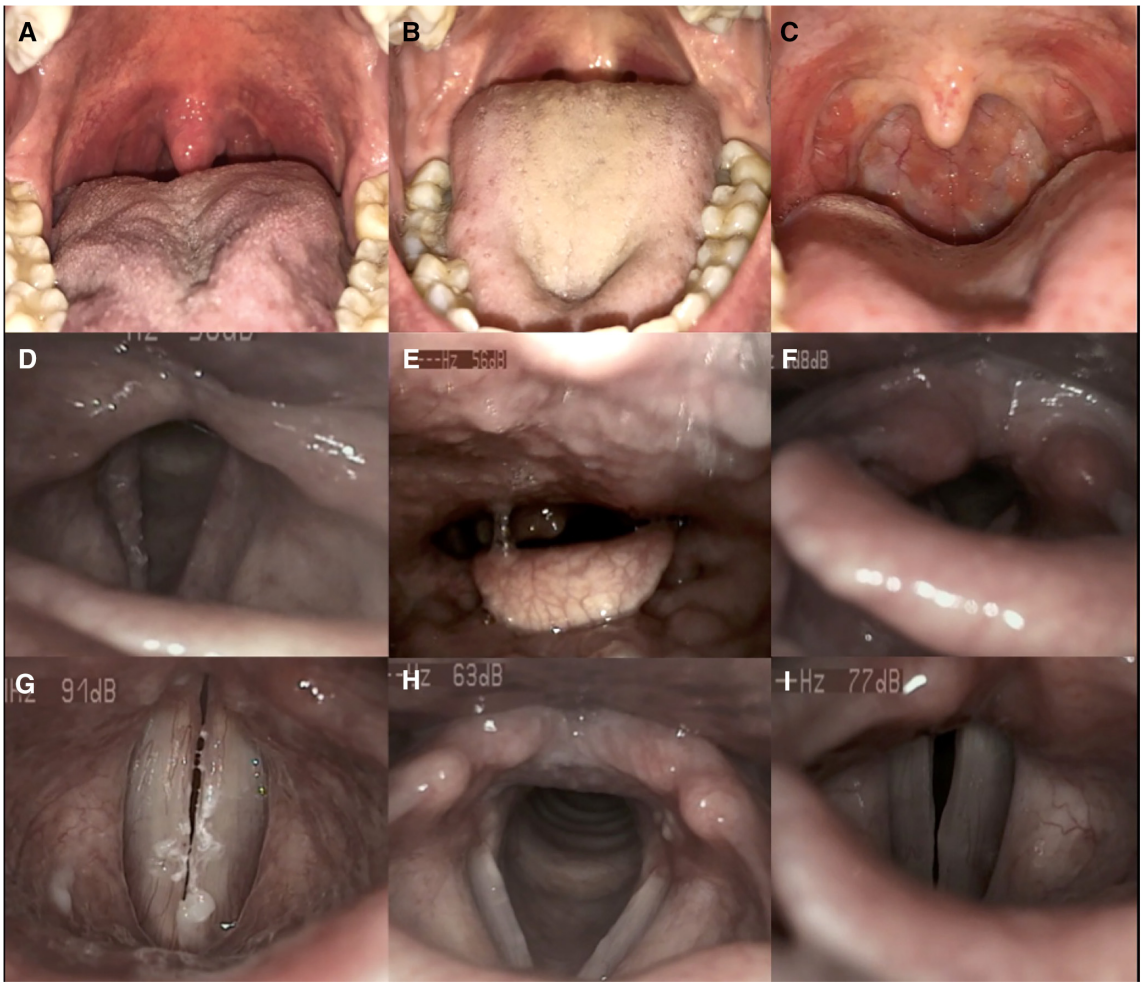

Fig. 3. Findings of Laryngopharyngeal reflux disease. Some forgotten signs of laryngopharyngeal reflux (videolaryngostroboscopic images): (A) redness of the oropharyngeal anterior pillars; (B) coated tongue (and redness of the oropharyngeal anterior pillars); (C) nodular inflammation of the posterior oropharyngeal wall; (D) vocal cord ulcerations; (E) tongue tonsil hypertrophy, sticky saliva, and nodularity of the posterior oropharyngeal wall; (F) hypertrophy of the posterior laryngeal wall and sticky saliva in piriform sinuses; (G) endolaryngeal sticky mucus; (H) keratosis of the vocal process of the left arytenoid cartilage; and (I) edema of the free edge of the left vocal fold.

TABLE V.
Recommendations for Future LPR Studies

Diagnosis Recommendations
1. To respect clear inclusion and exclusion criterias, including the exclusion of patients with many confounding conditions that may lead to laryngopharyngeal symptoms
2. To determine the incidence of all symptoms described in the current literature
3. To determine the incidence of all laryngeal and extralaryngeal signs described in the literature
4. To build new complete symptoms and signs instruments with assessment of severity and frequency of complaints
5. To determine the role of pH-impedance metry, oropharyngeal pH metry, and salivary detection of pepsin and trypsin
6. For the diagnosis, to develop multiparameter score including symptoms, signs, and pH/impedance findings
7. To determine the common and different clinical characteristics between nonacid, acid, and mixed LPR
8. To standardize the pharyngeal placement of probes of pH impedance metry and to standardize thresholds for the LPR diagnosis
Follow-up Recommendations
1. To use complete symptoms and signs scores, including the most prevalent clinical findings
2. For signs, to base the evaluation of each sign on a clear referential of severity (and not on subjective analog scale)
3. To consider both symptoms of LPR and GERD regarding their relationship
4. To determine the needed time to resolve all prevalent symptoms and signs related to LPR
Treatment Recommendations
1. To conduct multicenter placebo RCTs to definitively define the therapeutic efficiency of PPIs, alginate, magaldrate, and other drugs
2. To precisely assess the impact of diet and behavioral changes on the clinical improvement
3. To determine the adequate treatment scheme (e.g., diet, drugs, duration) according to types of LPR (acid, nonacid, mixed).

GERD = gastroeosophageal reflux disease; LPR = laryngopharyngeal reflux; PPIs = proton pump inhibitors; RCTs = controlled randomized trials.

15314995, 2019, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/lary.27591 by Thirion Paul - Dge, Wiley Online Library on [29/01/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Reflux Symptom Score

Within the last month, I suffered from one/several followed symptoms

Severity: 0= problem is not severe, 5 = problem very troublesome when it occurs

Frequency: 0= I don't have this complaint during the last month, 1;2;3;4 = I had 1-2;2-3;3-4;4-5 daily during the last week; 5= complaint occurs daily

	Disorder Frequency	Disorder Severity	Quality of Life impact
Ear Nose and Throat Disorders	Total score:…….	Total score:…….	Total score:…….
1. Hoarseness or a voice problem	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
2. Throat pain	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
3. Pain during swallowing time	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
4. Difficulty swallowing (pills, liquids or solid foods)	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
5. Clearing your throat	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
6. Sensation of something sticking in the throat	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
7. Excess mucous in the throat or postnasal drip sensation	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
8. Ear pressure/pain (daytime or nigh-time)	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
9. Tongue burning	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
10. Other: ……	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
Abdominal Disorders	Total score:…….	Total score:…….	Total score:…….
1. Heartburn, stomach acid coming up	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
2. Regurgitations of liquids, solid foods or burps	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
3. Abdominal pain	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
4. Diarrheas	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
5. Constipation	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
6. Indigestion	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
7. Abdominal distension and/or flatus	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
8. Halitosis	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
9. Nausea			
10. Other: ……	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
Chest/respiratory Disorders	Total score:…….	Total score:…….	Total score:…….
1. Cough after eating or lying down	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
2. Cough (daytime)	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
3. Breathing difficulties,breathlessness, or Wheezing	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
4. Chest pain			
5. Other: ……	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5	0 - 1 - 2 - 3 - 4 - 5
Do you think that this questionnaire well assesses your current complaints ?	YES - NO		

Fig. 4. Reflux Symptom Score. RSS is in the process of validation in French, English, and Italian. Symptoms are assessed within the last month. For each symptom, patient evaluates the occurrence of symptoms (1 = once a week; 2 = two or three times a week; 3 = four or five times a week; 4 = six times a week or almost every day; 5 = every day) and the severity of symptoms (1 = symptom is not severe, 5 = very severe when it occurs). RSS also assesses the impact of symptoms on quality of life (0 = no impact on my quality of life; 5 = significant impact on my quality of life). For each item, the severity score is multiplied by the frequency score. The sum of the results of these multiplications is calculated to have to RSS final score. The quality-of-life score is calculated separately. Three subcategories of RSS may be identified according to the affected system: ear, nose, and throat area versus intestinal area (gastroeosophageal disease) versus respiratory area (lung-associated diseases). Patient can add some unusual symptoms in subcategories of this tool. From these three subscores, future studies could develop thresholds indicating gastroenterological or chest examinations (i.e., gastroscopy, lung function tests). At the end of the questionnaire, all patients must assess whether the questionnaire includes all of the complaints. Additional complaints may be added.RSS = Reflux Symptom Score.

placebo RCTs interested in the impact of PPIs on LPR must take into consideration several key points. First is the elaboration of clear inclusion and exclusion criteria according to the diagnostic method used. Thereupon, in the case of failure to develop a gold standard diagnostic tool, the development of multi-parameter scores including symptoms, signs, pH monitoring findings, and some future new technologies could substantially improve the LPR diagnosis. Second, an improvement of the current tools used to assess both signs and symptoms is needed to exhaustively evaluate symptoms and signs related to LPR and gastroesophageal reflux disease that can be associated in a high number of patients.

15314995, 2019, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/lary.27591 by Thirion Paul - Dge, Wiley Online Library on [29/01/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Third, the role of diet and behavioral changes in the improvement of clinical findings must be clarified.

BIBLIOGRAPHY

1. Koufman JA, Aviv JE, Casiano RR, Shaw GY. Laryngopharyngeal reflux: position statement of the committee on speech, voice, and swallowing disorders of the American Academy of Otolaryngology–Head and Neck Surgery. *Otolaryngol Head Neck Surg* 2002;127:32–35.
2. Jin BJ, Lee YS, Jeong SW, Jeong JH, Lee SH, Tae K. Change of acoustic parameters before and after treatment in laryngopharyngeal reflux patients. *Laryngoscope* 2008;118:938–941.
3. Lee YS, Choi SH, Son YI, Park YH, Kim SY, Nam SY. Prospective, observational study using rabeprazole in 455 patients with laryngopharyngeal reflux disease. *Eur Arch Otorhinolaryngol* 2011;268:863–869.
4. Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. *Laryngoscope* 1991;101(suppl 53):1–78.
5. Wang J, Yu Z, Ren J, Xu Y, Zhang Y, Lei L, Zheng Y, Huang L, He Z. Effects of pepsin A on heat shock protein 70 response in laryngopharyngeal reflux patients with chronic rhinosinusitis. *Acta Oto-Laryngologica* 2017;137:848–854.
6. Book DT, Rhee JS, Toohill RJ, Smith TL. Perspectives in laryngopharyngeal reflux: an international survey. *Laryngoscope* 2002;112:1399–1406.
7. Lechien JR, Finck C, Khalife M, et al. Change of signs, symptoms and voice quality evaluations throughout a 3 to 6-months empirical treatment for laryngopharyngeal reflux disease. *Clin Otolaryngol* 2018;43: 1273–1282.
8. Falk GW. Laryngopharyngeal reflux: beauty is in the eye of the beholder. *Gastroenterology* 2007;133:1379–1381.
9. Hickson C, Simpson CB, Falcon R. Laryngeal pseudosulcus as a predictor of laryngopharyngeal reflux. *Laryngoscope* 2001;111:1742–1745.
10. Sataloff RT, Hawkshaw MJ, Gupta R. Laryngopharyngeal reflux and voice disorders: an overview on disease mechanisms, treatments, and research advances. *Discov Med* 2010;10:213–224.
11. Noordzij JP, Khidr A, Desper E, Meek RB, Reibel JF, Levine PA. Correlation of pH probe-measured laryngopharyngeal reflux with symptoms and signs of reflux laryngitis. *Laryngoscope* 2002;112:2192–2195.
12. Ford CN. Evaluation and management of laryngopharyngeal reflux. *JAMA* 2005;294:1534–1540.
13. Gupta N, Green RW, Megwalu UC. Evaluation of a laryngopharyngeal reflux management protocol. *Am J Otolaryngol* 2016;37:245–250.
14. Karkos PD, Wilson JA. Empiric treatment of laryngopharyngeal reflux with proton pump inhibitors: a systematic review. *Laryngoscope* 2006;116: 144–148.
15. Vaezi MF, Yang YX, Howden CW. Complications of proton pump inhibitor therapy. *Gastroenterology* 2017;153:35–48.
16. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
17. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383–394.
18. Systematic and literature review resources 2011. Available at: http://distillercer.com/resources. Accessed July 2015.
19. Cucherat M, Boissel JP, Leizorovicz A. *Meta-analyse des Essais Thérapeutiques*. Paris, France: Masson; 1997.
20. Havas T, Huang S, Levy M, et al. Posterior pharyngolaryngitis: double-blind randomised placebo-controlled trial of proton pump inhibitor therapy. *Aust J Otolaryngol* 1999;3:243–246.
21. El-Serag HB, Lee P, Buchner A, Inadomi JM, Gavin M, McCarthy DM. Lansoprazole treatment of patients with chronic idiopathic laryngitis: a placebo-controlled trial. *Am J Gastroenterol* 2001;96:979–983.
22. Langevin S, Ngo H. GERD-induced ENT symptoms: a prospective placebo controlled study with omeprazole 40 mg a day. *Gastroenterology* 2001;120-(suppl 1):A16.
23. Eherer AJ, Habermann W, Hammer HF, Kiesler K, Friedrich G, Krejs GJ. Effect of pantoprazole on the course of reflux-associated laryngitis: a placebo-controlled double-blind crossover study. *Scand J Gastroenterol* 2003;38:462–467.
24. Steward DL, Wilson KM, Kelly DH, et al. Proton pump inhibitor therapy for chronic laryngo-pharyngitis: a randomized placebo-control trial. *Otolaryngol Head Neck Surg* 2004;131:342–350.
25. Vaezi MF, Richter JE, Stasney CR, et al. Treatment of chronic posterior laryngitis with esomeprazole. *Laryngoscope* 2006;116:254–260.
26. Wo JM, Koopman J, Harrell SP, Parker K, Winstead W, Lentsch E. Double-blind, placebo-controlled trial with single-dose pantoprazole for laryngopharyngeal reflux. *Am J Gastroenterol* 2006;101:1972–1978; quiz 2169.
27. Reichel O, Dressel H, Wiederanders K, Issing WJ. Double-blind, placebo-controlled trial with esomeprazole for symptoms and signs associated with laryngopharyngeal reflux. *Otolaryngol Head Neck Surg* 2008; 139:414–420.
28. Vashani K, Murugesh M, Hattiangadi G, et al. Effectiveness of voice therapy in reflux-related voice disorders. *Dis Esophagus* 2010;23:27–32.
29. McGlashan JA, Johnstone LM, Sykes J, Strugala V, Dettmar PW. The value of a liquid alginate suspension (Gaviscon Advance) in the management of laryngopharyngeal reflux. *Eur Arch Otorhinolaryngol* 2009;266: 243–251.
30. Fass R, Noelck N, Willis MR, et al. The effect of esomeprazole 20 mg twice daily on acoustic and perception parameters of the voice in laryngopharyngeal reflux. *Neurogastroenterol Motil* 2010;22:134–141.
31. Lam PK, Ng ML, Cheung TK, et al. Rabeprazole is effective in treating laryngopharyngeal reflux in a randomized placebo-controlled trial. *Clin Gastroenterol Hepatol* 2010;8:770–776.
32. Ezzat WF, Fawaz SA, Fathey H, El Demerdash A. Virtue of adding prokinetics to proton pump inhibitors in the treatment of laryngopharyngeal reflux disease: prospective study. *J Otolaryngol Head Neck Surg* 2011;40: 350–356.
33. Tseng WH, Tseng PH, Wu JF, et al. Double-blind, placebo-controlled study with alginate suspension for laryngopharyngeal reflux disease. *Laryngoscope*. 2018. doi: 10.1002/lary.27111.
34. Siupsinskiene N, Adamonis K. Diagnostic test with omeprazole in patients with posterior laryngitis. *Medicina (Kaunas)* 2003;39:47–55.
35. Park W, Hicks DM, Khandwala F, et al. Laryngopharyngeal reflux: prospective cohort study evaluating optimal dose of proton-pump inhibitor therapy and pretherapy predictors of response. *Laryngoscope* 2005;115: 1230–1238.
36. Swoger J, Ponsky J, Hicks DM, et al. Surgical fundoplication in laryngopharyngeal reflux unresponsive to aggressive acid suppression: a controlled study. *Clin Gastroenterol Hepatol* 2006;4:433–441.
37. Hunchaisri N. Treatment of laryngopharyngeal reflux: a comparison between domperidone plus omeprazole and omeprazole alone. *J Med Assoc Thai* 2012;95:73–80.
38. Chung JW, Chun HJ, Lee MS, et al. Effect of stellate ganglion block on laryngopharyngeal reflux disease. *Korean J Anesthesiol* 2013;64:439–442.
39. Oridate N, Tokashiki R, Watanabe Y, Taguchi A, Kawamura O, Fujimoto K. Endoscopic laryngeal findings in Japanese patients with laryngopharyngeal reflux symptoms. *Int J Otolaryngol* 2012;2012:908154.
40. Chun BJ, Lee DS. The effect of itopride combined with lansoprazole in patients with laryngopharyngeal reflux disease. *Eur Arch Otorhinolaryngol* 2013;270:1385–1390.
41. Tokashiki R, Okamoto I, Funato N, Suzuki M. Rikkunshito improves globus sensation in patients with proton-pump inhibitor-refractory laryngopharyngeal reflux. *World J Gastroenterol* 2013;19:5118–5124.
42. Chappity P, Kumar R, Deka RC, Chokkalingam V, Saraya A, Sikka K. Proton pump inhibitors versus solitary lifestyle modification in management of laryngopharyngeal reflux and evaluating who is at risk: scenario in a developing country. *Clin Med Insights Ear Nose Throat*. 2014;7:1–5.
43. Wan Y, Yan Y, Ma F, et al. LPR: how different diagnostic tools shape the outcomes of treatment. *J Voice* 2014;28:362–368.
44. Ozturan O, Dogan R, Yenigun A, Veyseller B, Yildirim YS. Photographic objective alterations for laryngopharyngeal reflux diagnosis. *J Voice* 2017; 31:78–85.
45. Hanson DG, Kamel PL, Kahrilas PJ. Outcomes of antireflux therapy for the treatment of chronic laryngitis. *Ann Otol Rhinol Laryngol* 1995;104: 550–555.
46. Jaspersen D, Weber R, Hammar CH, Draf W. Effect of omeprazole on the course of associated esophagitis and laryngitis. *J Gastroenterol* 1996;31: 765–767.
47. Shaw GY, Searl JP. Laryngeal manifestations of gastroesophageal reflux before and after treatment with omeprazole. *South Med J* 1997;90: 1115–1122.
48. Wo JM, Grist WJ, Gussack G, Delgaudio JM, Waring JP. Empiric trial of high-dose omeprazole in patients with posterior laryngitis: a prospective study. *Am J Gastroenterol* 1997;92:2160–2165.
49. Metz DC, Childs ML, Ruiz C, Weinstein GS. Pilot study of the oral omeprazole test for reflux laryngitis. *Otolaryngol Head Neck Surg* 1997;116: 41–46.
50. Habermann W, Eherer A, Lindbichler F, Raith J, Friedrich G. Ex juvantibus approach for chronic posterior laryngitis: results of short-term pantoprazole therapy. *J Laryngol Otol* 1999;113:734–739.
51. Belafsky PC, Postma GN, Koufman JA. The validity and reliability of the reflux finding score (RFS). *Laryngoscope* 2001;111:1313–1317.
52. Hamdan AL, Sharara AI, Younes A, Fuleihan N. Effect of aggressive therapy on laryngeal symptoms and voice characteristics in patients with gastroesophageal reflux. *Acta Otolaryngol* 2001;121:868–872.
53. Rodriguez-Tellez M, Galera-Ruiz H, Arguelles-Arias F, et al. Posterior laryngitis: effects of treatment with omeprazole alone. *Rev Esp Enferm Dig* 2002;94:123–130.
54. Habermann W, Kiesler K, Eherer A, Friedrich G. Short-term therapeutic trial of proton pump inhibitors in suspected extraesophageal reflux. *J Voice* 2002;16:425–432.
55. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). *J Voice* 2002;16:274–277.
56. DelGaudio JM, Waring JP. Empiric esomeprazole in the treatment of laryngopharyngeal reflux. *Laryngoscope* 2003;113:598–601.
57. Bilgen C, Ogut F, Kesimli-Dinc H, Kirazli T, Bor S. The comparison of an empiric proton pump inhibitor trial vs 24-hour double-probe Ph monitoring in laryngopharyngeal reflux. *J Laryngol Otol* 2003;117:386–390.
58. Garrigues V, Gisbert L, Bastida G, et al. Manifestations of gastroesophageal reflux and response to omeprazole therapy in patients with chronic

15314995, 2019, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/lary.27591 by Thirion Paul - Dge, Wiley Online Library on [29/01/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

posterior laryngitis: an evaluation based on clinical practice. *Dig Dis Sci* 2003;48:2117–2123.
59. Beaver ME, Stasney CR, Weitzel E, et al. Diagnosis of laryngopharyngeal reflux disease with digital imaging. *Otolaryngol Head Neck Surg* 2003; 128:103–108.
60. Williams RB, Szczesniak MM, Maclean JC, Brake HM, Cole IE, Cook IJ. Predictors of outcome in an open label, therapeutic trial of high-dose omeprazole in laryngitis. *Am J Gastroenterol* 2004;99:777–785.
61. Issing WJ, Karkos PD, Perreas K, Folwaczny C, Reichel O. Dual-probe 24-hour ambulatory pH monitoring for diagnosis of laryngopharyngeal reflux. *J Laryngol Otol* 2004;118:845–848.
62. Sereg-Bahar M, Jansa R, Hocevar-Boltezar I. Voice disorders and gastroesophageal reflux. *Logoped Phoniatr Vocol* 2005;30:120–124.
63. Qadeer MA, Swoger J, Milstein C, et al. Correlation between symptoms and laryngeal signs in laryngopharyngeal reflux. *Laryngoscope* 2005;115: 1947–1952.
64. Dore MP, Pedroni A, Pes GM, et al. Effect of antisecretory therapy on atypical symptoms in gastroesophageal reflux disease. *Dig Dis Sci* 2007;52: 463–468.
65. Qua CS, Wong CH, Gopala K, Goh KL. Gastro-oesophageal reflux disease in chronic laryngitis: prevalence and response to acid-suppressive therapy. *Aliment Pharmacol Ther* 2007;25:287–295.
66. Oridate N, Takeda H, Asaka M, et al. Acid-suppression therapy offers varied laryngopharyngeal and esophageal symptom relief in laryngopharyngeal reflux patients. *Dig Dis Sci* 2008;53:2033–2038.
67. Chiba T, Kudara N, Abiko Y, et al. Effects of proton pump inhibitors in patients with laryngopharyngeal reflux disease. *Hepatogastroenterology* 2011; 58:1580–1582.
68. Koufman JA Low-acid diet for recalcitrant laryngopharyngeal reflux: therapeutic benefits and their implications. *Ann Otol Rhinol Laryngol* 2011; 120:281–287.
69. Masaany M, Marina MB, Sharifa Ezat WP, Sani A. Empirical treatment with pantoprazole as a diagnostic tool for symptomatic adult laryngopharyngeal reflux. *J Laryngol Otol* 2011;125:502–508.
70. Naiboglu B, Durmus R, Tek A, Toros SZ, Egeli E. Do the laryngopharyngeal symptoms and signs ameliorate by empiric treatment in patients with suspected laryngopharyngeal reflux? *Auris Nasus Larynx* 2011;38:622–627.
71. Patigaroo SA, Hashmi SF, Hasan SA, Ajmal MR, Mehfooz N. Clinical manifestations and role of proton pump inhibitors in the management of laryngopharyngeal reflux. *Indian J Otolaryngol Head Neck Surg* 2011;63: 182–189.
72. Habermann W, Schmid C, Neumann K, Devaney T, Hammer HF. Reflux symptom index and reflux finding score in otolaryngologic practice. *J Voice* 2012;26:e123–e127.
73. Park JO, Shim MR, Hwang YS, et al. Combination of voice therapy and antireflux therapy rapidly recovers voice-related symptoms in laryngopharyngeal reflux patients. *Otolaryngol Head Neck Surg* 2012;146:92–97.
74. Becker V, Graf S, Schlag C, et al. First agreement analysis and day-to-day comparison of pharyngeal pH monitoring with pH/impedance monitoring in patients with suspected laryngopharyngeal reflux. *J Gastrointest Surg* 2012;16:1096–1101.
75. Lien HC, Wang CC, Lee SW, et al. Responder definition of a patient-reported outcome instrument for laryngopharyngeal reflux based on the US FDA guidance. *Value Health* 2015;18:396–403.
76. Beech TJ, Campbell G, McDermott AL, Batch AJ. The effect of anti-reflux treatment on subjective voice measurements of patients with laryngopharyngeal reflux. *J Laryngol Otol* 2013;127:590–594.
77. Vailati C, Mazzoleni G, Bondi S, Bussi M, Testoni PA, Passaretti S. Oropharyngeal pH monitoring for laryngopharyngeal reflux: is it a reliable test before therapy? *J Voice* 2013;27:84–89.
78. Lee JS, Lee YC, Kim SW, Kwon KH, Eun YG. Changes in the quality of life of patients with laryngopharyngeal reflux after treatment. *J Voice* 2014; 28:487–491.
79. Semmanaselvan K, Mukaddam QI, Naik M. An open label, prospective, single centre study to evaluate the efficacy and safety of fixed dose combination of rabeprazole (enteric-coated, EC) 20 mg + domperidone (sustained release, SR) 30 mg capsule in treatment of patients with laryngopharyngeal reflux disease. *J Assoc Physicians India* 2015;63:27–32.
80. Batıoglu-Karaaltın A, Develioglu ON, Tarhan O, Kulekci M. The importance of voice analysis in evaluating the effectiveness of reflux treatment. *Kulak Burun Bogaz Ihtis Derg* 2016;26:207–212.
81. Dulery C, Lechot A, Roman S, et al. A study with pharyngeal and esophageal 24-hour pH-impedance monitoring in patients with laryngopharyngeal symptoms refractory to proton pump inhibitors. *Neurogastroenterol Motil* 2017. doi: 10.1111/nmo.12909.
82. Joshi AA, Chiplunkar BG, Bradoo RA. Assessment of treatment response in patients with laryngopharyngeal reflux. *Indian J Otolaryngol Head Neck Surg* 2017;69:77–80.
83. Pullarat AN, Attakkil A, Sibin. MA, Nayak DR, Pillai S. Hoarseness and laryngopharyngeal reflux: a prospective study. *IOSR J Dent Med Sci* 2017;16:41–50.
84. Friedman M, Maley A, Kelley K, Pulver T, Foster M, Fisher M, Joseph N. Impact of pH monitoring on laryngopharyngeal reflux treatment: improved compliance and symptom resolution. *Otolaryngol Head Neck Surg* 2011;144:558–562.
85. Waxman J, Yalamanchali S, Valle ES, Pott T, Friedman M. Effects of proton pump inhibitor therapy for laryngopharyngeal reflux on posttreatment symptoms and hypopharyngeal pH. *Otolaryngol Head Neck Surg* 2014;150:1010–1017.
86. Nennstiel S, Andrea M, Abdelhafez M, et al. pH/multichannel impedance monitoring in patients with laryngo-pharyngeal reflux symptoms: prediction of therapy response in long-term follow-up. *Arab J Gastroenterol* 2016;17:113–116.
87. Lechien JR, Huet K, Finck C, et al. Validity and reliability of a French version of reflux symptom index. *J Voice* 2017;31:512.e1–512.e7.
88. Lechien JR, Huet K, Khalife M, et al. Impact of laryngopharyngeal reflux on subjective and objective voice assessments: a prospective study. *J Otolaryngol Head Neck Surg*. 2016;45:59.
89. Shaw GY, Searl JP, Young JL, Miner PB. Subjective, laryngoscopic, and acoustic measurements of laryngeal reflux before and after treatment with omeprazole. *J Voice* 1996;10:410–418.
90. Lee YC, Lee JS, Kim SW, Kwon KH, Eun YG. Influence of age on treatment with proton pump inhibitors in patients with laryngopharyngeal reflux disease: a prospective multicenter study. *JAMA Otolaryngol Head Neck Surg* 2013;139:1291–1295.
91. Shin MH, Nam SY, Park YH, Son YI. Open-label observational study for evaluating the short-term benefits of rabeprazole medication on laryngopharyngeal reflux. *Clin Exp Otorhinolaryngol* 2012;5:28–33.
92. Oridate N, Takeda H, Mesuda Y, et al. Evaluation of upper abdominal symptoms using the frequency scale for the symptoms of gastroesophageal reflux disease in patients with laryngopharyngeal reflux symptoms. *J Gastroenterol* 2008;43:519–523.
93. Guo H, Ma H, Wang J. Proton pump inhibitor therapy for the treatment of laryngopharyngeal reflux: a meta-analysis of randomized controlled trials. *J Clin Gastroenterol* 2016;50:295–300.
94. Shaheen NJ, Crockett SD, Bright SD, et al. Randomised clinical trial: high-dose acid suppression for chronic cough—a double-blind, placebo-controlled study. *Aliment Pharmacol Ther* 2011;33:225–234.
95. Ours TM, Kavuru MS, Schilz RJ, et al. A prospective evaluation of esophageal testing and a double-blind, randomized study of omeprazole in a diagnostic and therapeutic algorithm for chronic cough. *Am J Gastroenterol* 1999;94:3131–3138.
96. Schmid CH. Exploring heterogeneity in randomized trials via meta-analysis. *Ther Innov Regul Sci* 1999;33:211–224
97. Yang LJ, Chang KW, Chung KC. Methodologically rigorous clinical research. *Plast Reconstr Surg* 2012;129:979e–988e.
98. Eren E, Arslanoglu S, Aktas A, et al. Factors confusing the diagnosis of laryngopharyngeal reflux: the role of allergic rhinitis and inter-rater variability of laryngeal findings. *Eur Arch Otorhinolaryngol* 2014;271: 743–747.
99. Altundag A, Cayonu M, Salihoglu M, Yazıcı H, Kurt O, Yalcınkaya E, Saglam O. Laryngopharyngeal reflux has negative effects on taste and smell functions. *Otolaryngol Head Neck Surg* 2016;155:117–121.
100. Lou Z. Assessment of laryngopharyngeal reflux and the shape of the Eustachian tube should be considered in chronic rhinosinusitis with nasal polyps and chronic otitis media. *Eur Arch Otorhinolaryngol* 2017;274: 4265–4266.
101. Aydın E, Tastan E, Aydogan F, Arslan N, Karaca G. Role of nasopharyngeal reflux in the etiology of otitis media with effusion. *J Otolaryngol Head Neck Surg* 2011;40:499–503.
102. Remacle M, Lawson G. Diagnosis and management of laryngopharyngeal reflux disease. *Curr Opin Otolaryngol Head Neck Surg* 2006;14:143–149.
103. Harris MS, Rotenberg BW, Roth K, Sowerby LJ. Factors associated with lingual tonsil hypertrophy in Canadian adults. *J Otolaryngol Head Neck Surg* 2017;46:32.
104. Hill RK, Simpson CB, Velazquez R, Larson N. Pachydermia is not diagnostic of active laryngopharyngeal reflux disease. *Laryngoscope* 2004;114: 1557–1561.
105. Chang BA, MacNeil SD, Morrison MD, Lee PK. The reliability of the reflux finding score among general otolaryngologists. *J Voice* 2015; 29:572–577.
106. Musser J, Kelchner L, Neils-Strunjas J, Montrose M. A comparison of rating scales used in the diagnosis of extraesophageal reflux. *J Voice* 2011; 25:293–300.
107. Kajii Y, Shingai T, Kitagawa J, et al. Sour taste stimulation facilitates reflex swallowing from the pharynx and larynx in the rat. *Physiol Behav* 2002;77:321–325.
108. Aviv JE, Liu H, Parides M, Kaplan ST, Close LG. Laryngopharyngeal sensory deficits in patients with laryngopharyngeal reflux and dysphagia. *Ann Otol Rhinol Laryngol*. 2000;109:1000–1006.
109. Eskiizmir G, Kezirian E. Is there a vicious cycle between obstructive sleep apnea and laryngopharyngeal reflux disease? *Med Hypotheses* 2009;73: 706–708.
110. Harding SM, Richter JE. The role of gastroesophageal reflux in chronic cough and asthma. *Chest* 1997;111:1389–1402.
111. Ing AJ. Interstitial lung disease and gastroesophageal reflux. *Am J Med* 2001;111(suppl 8A):41S–44S.
112. Lechien JR, Saussez S, Harmegnies B, Finck C, Burns JA. Laryngopharyngeal reflux and voice disorders: a multifactorial model of etiology and pathophysiology. *J Voice* 2017;31:733–752.
113. Lechien JR, Finck C, Costa de Araujo P, et al. Voice outcomes of laryngopharyngeal reflux treatment: a systematic review of 1483 patients. *Eur Arch Otorhinolaryngol* 2017;274:1–23.
114. Altman KW, Prufer N, Vaezi MF. A review of clinical practice guidelines for reflux disease: toward creating a clinical protocol for the otolaryngologist. *Laryngoscope* 2011;121:717–723.
115. Reimer C, Bytzer P. Management of laryngopharyngeal reflux with proton pump inhibitors. *Ther Clin Risk Manag* 2008;4:225–233.

15314995, 2019, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/lary.27591 by Thirion Paul - Dge, Wiley Online Library on [29/01/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License