



Supplementary Figure 1 Improved multidimensional quality of life as demonstrated by a disease specific patient-reported outcome instrument in three potential of hydrogen (+) groups after proton pump inhibitor treatment, compared to potential of hydrogen (-) group. pH: Potential of hydrogen; PAR: Pharyngeal acid reflux; EAR: Esophageal acid reflux.

Supplementary Table 1 Exclusion criteria

Exclusion criteria

Respiratory or gastrointestinal malignancy

Receiving radiation therapy, surgery or trauma for the respiratory or upper gastrointestinal tract

Current smoker, or history of previous heavy smoking or substance or alcohol abuse

Infectious laryngitis in the previous 3 months

Exposure to environmental irritants in the past 3 months

Vocal cord papilloma, enlarged lingual or palatine tonsils, or goiter

Excessive voice use

Bronchial asthma

Chronic cough attributable to angiotensin-converting enzyme inhibitor, or known chronic pulmonary or tracheobronchial etiologies, such as eosinophilic bronchitis, bronchiectasis, positive methacholine provocation test result, or response to inhaled or systemic steroid

Pharyngeal (Zenker's) diverticulum or esophageal stasis syndrome, such as achalasia

Anxiety or depression with positive response or improvement after 1 month of treatment with an anxiolytic or an antidepressant

Chronic or allergic rhinosinusitis, nasal polyposis, or postnasal drip that is responsive to at least 1 month of medical therapy with antihistamine, topical steroid spray, or defined by nasal endoscopy or computed tomography scan

Participation in another investigational drug study in the previous month

Acid suppressive therapy within 4 weeks before recruitment

Need for continuous therapy with theophylline, iron supplements, warfarin, antifungal drugs, and digitalis, or a history of previous allergy to any ppis

Women during pregnancy or lactation, or inability to maintain effective contraception if of child-bearing potential

A serious illness that might interfere with study participation

Inability to fill out the questionnaires or refusal to participate

Supplementary Table 2 Baseline reflux finding score by item

Reflux finding score, median (interquartile range)	PAR ¹ alone (n = 11)	EAR ² alone (n = 68)	Both pH (+) (n = 18)	Both pH (-) (n = 93)	P value (4-group comparison)
Subglottic edema	0 (0, 0)	0 (0, 2) ^{3,4}	0 (0, 0)	0 (0, 2)	0.03
Ventricular obliteration	2 (1, 4)	0 (0, 2)	0 (0, 2)	2 (0, 2)	0.08
Erythema/hyperemia	0 (0, 2)	2 (0, 2)	0 (0, 2)	2 (0, 2)	0.3
Vocal fold edema	1 (1, 1)	1 (1, 1)	1 (0, 1)	1 (1, 1)	0.4
Diffuse laryngeal edema	1 (1, 1)	1 (1, 1)	1 (0, 1)	1 (1, 1)	0.08
Posterior commissure hypertrophy	2 (1, 2)	1 (1, 2)	1 (1, 2)	1 (1, 2)	0.8
Granuloma/granulation	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.4
Thick endolaryngeal mucus	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 2)	0.04

¹Excessive pharyngeal acid reflux is defined as pharyngeal acid reflux ≥ 2 episodes.

²Excessive distal esophageal acid reflux is defined as distal esophageal acid reflux total time $\geq 4.2\%$ of 24-hour, or $\geq 6.3\%$ of upright position, or $\geq 1.2\%$ of supine position.

³ $P < 0.05$ for esophageal acid reflux alone vs both potential of hydrogen (-).

⁴ $P < 0.05$ for esophageal acid reflux alone vs both potential of hydrogen (+).

Supplementary Table 3 Univariate and multivariate logistic regression for prediction of proton pump inhibitors responders

	PPI responders (<i>n</i> = 89)	PPI responders (<i>n</i> = 101)	non- PPI (<i>n</i> = 101)	<i>P</i> value	Multivariate analysis aOR (95% CI)	<i>P</i> value
Demography, <i>n</i> (%)						
Age ≥ 50 years	56 (63)	56 (55)		0.4	1.2 (0.6-2.3)	0.6
Male gender	53 (60)	62 (61)		0.8	0.8 (0.4-1.6)	0.6
BMI ≥ 24 kg/m ²	41 (46)	50 (50)		0.7	0.7 (0.4-1.3)	0.2
ENT first visit	69 (78)	75 (74)		0.7		
Clinical presentations						
Major laryngeal symptom, <i>n</i> (%)				0.01		
Globus sensation	13 (15)	37 (37)				
Throat pain	25 (28)	17 (17)				

Hoarseness	28 (31)	28 (28)			
Cough	15 (17)	11 (11)			
Throat clearing	8 (9)	8 (8)			
Symptom duration, median (IQR), months	13 (6, 42)	18 (12, 36)	0.4		
Typical reflux symptoms ³ , <i>n</i> (%)	48 (54)	51 (50)	0.7		
Previous acid suppressive therapy use, <i>n</i> (%)	53 (63)	60 (60)	0.8		
Diabetes mellitus, <i>n</i> (%)	2 (2)	7 (7)	0.2		
Hypertension, <i>n</i> (%)	17 (19)	20 (20)	0.9		
Post nasal drip, <i>n</i> (%)	32 (36)	49 (49)	0.09		
Endoscopic findings					
Reflux esophagitis, <i>n</i> (%)	9 (10)	14 (14)	0.6	0.3 (0.1-0.9)	0.02
Barrett's esophagus, <i>n</i> (%)	3 (3)	4 (4)	0.9		
Hiatus hernia, <i>n</i> (%)	11 (12)	13 (13)	0.9		
Peptic ulcer, <i>n</i> (%)	13 (15)	10 (10)	0.4		
<i>Helicobacter pylori</i> , <i>n</i> (%)	8 (12)	26 (31)	0.007		
Reflux Finding Score ⁴ , median (IQR)	7 (5, 10)	7 (4, 10)	0.8		
24h pH finding					

Distal esophagus, median (IQR)				
Total time pH < 4	3.5 (0.9, 6.4)	1.5 (0.3, 5.1)		0.008
Upright time pH < 4	4.5 (1.2, 9)	2.1 (0.4, 6.6)		0.01
Supine time pH < 4	0.1 (0.0, 1.8)	0.0 (0.0, 0.7)		0.09
Pharynx, median (IQR)				
Number of PAR event, total	0 (0, 1)	0 (0, 0)		0.1
Number of PAR event, upright	0 (0, 1)	0 (0, 0)		0.1
Number of PAR event, supine	0 (0, 0)	0 (0, 0)		0.4
EAR (+) ² , <i>n</i> (%)	50 (56)	36 (36)		0.007
PAR (+) ¹ , <i>n</i> (%)	18 (20)	11 (11)		0.1
EAR (+) ² and/or PAR (+) ¹ , <i>n</i> (%)	58 (65)	39 (39)		0.0005
pH test, <i>n</i> (%)				0.003
Both pH (-)	31 (35)	62 (61)	1.0 (Ref.)	
PAR ¹ alone	8 (9)	3 (3)	7.4 (1.7-32.7)	0.008
EAR ² alone	40 (45)	28 (28)	4.2 (2.0-8.8)	0.0002
Both pH (+)	10 (11)	8 (8)	3.4 (1.1-10.1)	0.03
Manometry finding				
Lower esophageal sphincter, median (IQR),	15 (9, 27)	16 (10, 26)		0.3

mmHg			
Upper esophageal sphincter, median (IQR),	32 (17, 55)	36 (23, 70)	0.3
mmHg			
Ineffective esophageal motility, <i>n</i> (%)	15 (26)	16 (28)	0.9
Esophageal sensation, <i>n</i> (%)			
Bernstein test	23 (26)	24 (24)	0.8
Symptom index	28 (31)	28 (28)	0.7
Patient report outcome, median (IQR)			
Reflux Symptom Index total score ⁵	17 (10, 20)	16 (12, 23)	0.5
GERDyzer total score ⁶	35 (25, 47)	42 (30, 53)	0.06
Heartburn, frequency ⁷	2 (0, 4)	1 (0, 4)	0.6
Heartburn, severity ⁷	2 (0, 3)	2 (0, 3)	0.9
Acid regurgitation, frequency ⁷	3 (1, 5)	2 (1, 4)	0.4
Acid regurgitation, severity ⁷	2 (1, 4)	3 (1, 4)	0.6

¹Excessive pharyngeal acid reflux is defined as pharyngeal acid reflux ≥ 2 episodes.

²Excessive distal esophageal acid reflux is defined as distal esophageal acid reflux total time $\geq 4.2\%$ of 24-hour, or $\geq 6.3\%$ of upright position,

or $\geq 1.2\%$ of supine position.

³Typical reflux symptoms is defined as regurgitation or heartburn at least twice a week with mild symptom, or once a week with moderate/severe symptom.

⁴Score range from 0 to 26, with higher scores suggesting more severe laryngitis.

⁵Score range from 0 to 45, with higher scores suggesting more severe symptoms.

⁶Score range from 0 to 70, with higher scores suggesting worse quality of life.

⁷Score range from 0 to 5 for symptom frequency or severity, with higher scores suggesting worse quality of life.

PAR: Pharyngeal acid reflux; EAR: Esophageal acid reflux; pH: Potential of hydrogen; BMI: Body mass index; ENT: Ear-nose-throat specialists; GERD: Gastroesophageal reflux disease; IQR: Interquartile range; PPI: Proton pump inhibitors.

Supplementary Table 4 Primary outcomes of each major laryngeal symptom

	PAR ¹ alone (<i>n</i> = 11)	EAR ² alone (<i>n</i> = 68)	Both pH (+) (<i>n</i> = 18)	Both pH (-) (<i>n</i> = 93)	<i>P</i> value (4-group comparison)
Globus sensation					
<i>n</i>	1	17	6	26	
Week 4					
Symptom improvement, median (IQR)	0 (0, 0)	30 (0, 50) ³	20 (0, 30)	0 (0, 20)	0.1

≥ 50% improvement, <i>n</i> (%)	0 (0)	8 (47)	1 (17)	5 (19)	0.2
Week 8					
Symptom improvement, median (IQR)	0 (0, 0)	50 (30, 70) ³	0 (0, 30)	10 (0, 40)	0.03
≥ 50% improvement, <i>n</i> (%)	0 (0)	10 (59) ³	1 (17)	6 (23)	0.06
Week 12					
Symptom improvement, median (IQR)	0 (0, 0)	30 (0, 70)	35 (0, 50)	0 (0, 35)	0.3
≥ 50% improvement, <i>n</i> (%)	0 (0)	7 (41)	2 (33)	4 (15)	0.3
Throat pain					
<i>n</i>	2	18	4	18	
Week 4					
Symptom improvement, median (IQR)	45 (40, 50)	30 (0, 75)	10 (0, 53)	25 (0, 60)	0.9
≥ 50% improvement, <i>n</i> (%)	1 (50)	8 (44)	1 (25)	8 (44)	0.9
Week 8					
Symptom improvement, median (IQR)	75 (70, 80)	49 (30, 80)	40 (0, 90)	30 (0, 90)	0.8

≥ 50% improvement, <i>n</i> (%)			2 (100)	9 (50)	2 (50)	8 (47)	0.6
Week 12							
Symptom improvement, median (IQR)			85 (80, 90)	55 (0, 80)	50 (0, 100)	60 (0, 90)	0.7
≥ 50% improvement, <i>n</i> (%)			2 (100)	10 (56)	2 (50)	11 (61)	0.6
Hoarseness							
<i>n</i>			3	18	5	30	
Week 4							
Symptom improvement, median (IQR)			20 (0, 70)	18 (0, 50)	30 (30, 30)	0 (0, 20)	0.2
≥ 50% improvement, <i>n</i> (%)			1 (33)	5 (28)	1 (20)	3 (10)	0.4
Week 8							
Symptom improvement, median (IQR)			60 (20, 70)	50 (10, 80) ³	50 (20, 60)	20 (0, 50)	0.1
≥ 50% improvement, <i>n</i> (%)			2 (67)	11 (65)	3 (60)	11 (37)	0.2
Week 12							
Symptom improvement, median (IQR)			85 (20, 100)	70 (30, 90) ³	50 (50, 90)	30 (0, 50)	0.02

≥ 50% improvement, <i>n</i> (%)	2 (67)	12 (67)	4 (80)	10 (33)	0.06
Cough					
<i>n</i>	5	11	2	8	
Week 4					
Symptom improvement, median (IQR)	66 (20, 90)	50 (30, 90) ³	45 (40, 50)	5 (0, 35)	0.1
≥ 50% improvement, <i>n</i> (%)	3 (60)	6 (55)	1 (50)	2 (25)	0.5
Week 8					
Symptom improvement, median (IQR)	80 (70, 90)	60 (30, 98)	40 (40, 40)	25 (0, 45)	0.2
≥ 50% improvement, <i>n</i> (%)	4 (80)	8 (73)	0 (0)	2 (25)	0.047
Week 12					
Symptom improvement, median (IQR)	90 (50, 99)	80 (40, 100)	40 (30, 50)	40 (20, 58)	0.7
≥ 50% improvement, <i>n</i> (%)	4 (80)	8 (73)	1 (50)	2 (25)	0.1
Throat clearing					
<i>n</i>	0	4	1	11	
Week 4					

Symptom improvement, median (IQR)	30 (15, 60)	30 (30, 30)	10 (0, 30)	0.2
≥ 50% improvement, <i>n</i> (%)	1 (25)	0 (0)	1 (9)	0.7
Week 8				
Symptom improvement, median (IQR)	45 (20, 65)	60 (60, 60)	30 (0, 50)	0.5
≥ 50% improvement, <i>n</i> (%)	2 (50)	1 (100)	4 (36)	0.5
Week 12				
Symptom improvement, median (IQR)	55 (25, 75)	80 (80, 80)	30 (10, 60)	0.4
≥ 50% improvement, <i>n</i> (%)	3 (75)	1 (100)	4 (36)	0.2

¹Excessive pharyngeal acid reflux is defined as pharyngeal acid reflux ≥ 2 episodes.

²Excessive distal esophageal acid reflux is defined as distal esophageal acid reflux total time $\geq 4.2\%$ of 24-hour, or $\geq 6.3\%$ of upright position, or $\geq 1.2\%$ of supine position.

³ $P < 0.05$ for esophageal acid reflux alone *vs* both potential of hydrogen (-).

PAR: Pharyngeal acid reflux; EAR: Esophageal acid reflux; pH: Potential of hydrogen; IQR: Interquartile range.

Supplementary Table 5 Symptom scores of heartburn and acid regurgitation

	PAR ¹ alone (n = 11)	EAR ² alone (n = 68)	Both pH (+) (n = 18)	Both pH (-) (n = 93)	P value (4-group comparison)
Week 4, median (IQR)					
Heartburn, frequency	1 (0, 3)	0 (0, 1) ^{3,4}	2 (0, 3)	1 (0, 3)	0.06
Heartburn, severity	1 (0, 2)	0 (0, 2)	1 (0, 3)	1 (0, 2)	0.3
Acid regurgitation, frequency	2 (1, 3)	1 (0, 2) ^{3,4}	3 (1, 3)	2 (0, 3)	0.007
Acid regurgitation, severity	2 (1, 2)	1 (0, 2) ^{3,4}	2 (1, 3)	1 (0, 3)	0.03
Week 8, median (IQR)					
Heartburn, frequency	0 (0, 1)	0 (0, 1)	1 (0, 2)	1 (0, 2)	0.4
Heartburn, severity	1 (0, 2)	0 (0, 2)	1 (0, 2)	1 (0, 2)	0.7
Acid regurgitation, frequency	1 (0, 2)	0 (0, 2) ^{3,4}	2 (0, 3)	1 (0, 3)	0.04
Acid regurgitation, severity	2 (0, 2)	1 (0, 2) ³	1 (0, 2)	1 (0, 2)	0.09
Week 12, median (IQR)					
Heartburn, frequency	1 (0, 2)	0 (0, 1) ³	1 (0, 2)	1 (0, 3)	0.2
Heartburn, severity	1 (0, 2)	0 (0, 1) ³	0 (0, 1)	1 (0, 2)	0.2
Acid regurgitation, frequency	1 (0, 2)	0 (0, 1) ^{3,4}	1 (0, 3)	1 (0, 3)	0.0007
Acid regurgitation, severity	1 (0, 2)	0 (0, 1) ³	1 (0, 2)	1 (0, 3)	0.008

¹Excessive pharyngeal acid reflux is defined as pharyngeal acid reflux ≥ 2 episodes.

²Excessive distal esophageal acid reflux is defined as distal esophageal acid reflux total time $\geq 4.2\%$ of 24-hour, or $\geq 6.3\%$ of upright position, or $\geq 1.2\%$ of supine position.

³ $P < 0.05$ for esophageal acid reflux alone *vs* both potential of hydrogen (-).

⁴ $P < 0.05$ for esophageal acid reflux alone *vs* both potential of hydrogen (+).

PAR: Pharyngeal acid reflux; EAR: Esophageal acid reflux; pH: Potential of hydrogen; IQR: Interquartile range.

Supplementary Table 6 Manometric and 24 hours potential of hydrogen findings where pathological pharyngeal acid reflux is defined as pharyngeal acid reflux ≥ 1 episodes

	PAR ¹ alone (<i>n</i> = 17)	EAR ² alone (<i>n</i> = 52)	Both pH (+) (<i>n</i> = 34)	Both pH (-) (<i>n</i> = 87)	<i>P</i> value (4-group comparison)
24 hours pH findings, median (IQR)					
Distal esophagus					
Total time pH < 4	1.6 (0.9, 2.3) ^{3,6,7}	5.7 (4.2, 8.5) ^{4,8}	7.4 (4.7, 10.9) ⁵	0.6 (0.1, 1.3)	<0.0001
Upright time pH < 4	2.4 (1.4, 3.5) ^{3,6,7}	8 (4.9, 11.8) ⁴	9.8 (6.6, 12.7) ⁵	0.7 (0.2, 2.0)	<0.0001
Supine time pH < 4	0.0 (0.0, 0.1) ^{6,7}	1.2 (0.0, 4.3) ⁴	1.9 (0.3, 7.4) ⁵	0.0 (0.0, 0.0)	<0.0001
Pharynx					
Number of PAR event, total	2 (1, 5) ^{3,6}	0 (0, 0) ⁸	2 (1, 3) ⁵	0 (0, 0)	<0.0001

Number of PAR event, upright	2 (1, 5) ^{3,6}	0 (0, 0) ⁸	2 (1, 3) ⁵	0 (0, 0)	<0.0001
Number of PAR event, supine	0 (0, 0) ^{3,6}	0 (0, 0) ⁸	0 (0, 0) ⁵	0 (0, 0)	0.0003
Manometric findings					
Lower esophageal sphincter, median (IQR), mmHg	16 (10, 21)	14 (10, 20) ⁸	10 (7, 15) ⁵	16 (10, 28)	0.001
Upper esophageal sphincter, median (IQR), mmHg	32 (25, 71)	30 (17, 47)	20 (11, 35) ⁵	38 (25, 54)	0.003
Ineffective esophageal motility, <i>n</i> (%)	1 (8.33)	8 (25)	5 (23.8)	11 (22)	0.7
Esophageal sensation, <i>n</i> (%)					
Bernstein test	5 (31)	12 (23) ⁸	18 (56) ⁵	14 (16)	0.0002
Symptom index	6 (35)	18 (34) ⁴	18 (55) ⁵	14 (16)	0.0004
Symptom improvement, median (IQR)					
Week 4	20 (0, 50)	30 (0, 60) ⁴	30 (10, 50) ⁵	0 (0, 30)	0.011
Week 8	60 (20, 70)	50 (15, 80) ⁴	49 (0, 70)	20 (0, 50)	0.007
Week 12	50 (0, 90)	60 (20, 80) ⁴	50 (0, 90)	30 (0, 60)	0.02
Symptom improvement ≥ 50%, <i>n</i> (%)					
Week 4	5 (30)	19 (37)	13 (38)	19 (22)	0.2
Week 8	9 (53)	30 (58) ⁴	17 (50)	30 (35)	0.04

Total time pH < 4, median (IQR)	0.1 (0.0, 0.5) ⁷		0.3 (0.1, 1.1) ^{4,8}	-	4.2 (1.0, 4.5) ⁵		0.0 (0.0, 0.1)	
Upright time pH < 4, median (IQR)	0.1 (0.0, 0.8)		0.4 (0.1, 1.2) ⁴	-	1.0 (0.3, 1.5) ⁵		0.0 (0.0, 0.1)	
Supine time pH < 4, median (IQR)	0.1 (0.0, 0.2) ³		0.0 (0.0, 0.1) ^{4,8}	-	7.5 (0.3, 9.3) ⁵		0.0 (0.0, 0.0)	
Number of acid reflux events	7 (3, 11) ³	14 (5, 28) ³	0 (0, 0)	13 (4, 20) ⁴	3 (2, 5) ⁵	29 (24, 33) ⁵	0 (0, 0)	4 (1, 8)
Number of total events		23 (20, 31) ³		23 (15, 31) ⁴		36 (31, 55) ⁵		11 (7, 17)
Pharynx, median (IQR)								
Number of PAR event, total	7 (3, 11) ^{3,6}	2 (2, 5) ^{3,6}	0 (0, 0) ^{4,8}	0 (0, 0)	3 (2, 5) ⁵	3 (2, 7) ⁵	0 (0, 0)	0 (0, 0)
Number of PAR event, upright	7 (2, 10) ^{3,6}	2 (2, 5) ^{3,6}	0 (0, 0) ^{4,8}	0 (0, 0)	3 (2, 5) ⁵	3 (2, 7) ⁵	0 (0, 0)	0 (0, 0)
Number of PAR event, supine	0 (0, 1) ^{3,6}	0 (0, 0)	0 (0, 0) ⁸	0 (0, 0)	0 (0, 0) ⁵	0 (0, 0) ⁵	0 (0, 0)	0 (0, 0)

Symptom improvement, median (IQR)									
Week 4	30 (10, 70)	66 (5, 70) ³	45 (10, 70) ⁴	20 (0, 50) ⁴	30 (20, 30)	30 (0, 75)	0 (0, 50)	0 (0, 20)	
Week 8	70 (40, 80)	70 (0, 92)	60 (40, 90) ^{4,8}	50 (10, 70) ⁴	20 (0, 60)	50 (0, 100)	20 (0, 68)	20 (0, 50)	
Week 12	83 (35, 90)	100 (0, 100)	67 (20, 90) ⁴	55 (0, 70) ⁴	50 (0, 90)	50 (0, 99)	30 (0, 65)	30 (0, 50)	
Symptom improvement \geq 50%, <i>n</i> (%)									
Week 4	3 (38)	2 (67)	17 (50)	11 (32) ⁴	2 (18)	2 (29)	13 (33)	6 (12)	
Week 8	6 (75)	2 (67)	22 (67) ^{4,8}	18 (53) ⁴	3 (27)	4 (57)	16 (40)	15 (29)	
Week 12	6 (75)	2 (67)	20 (59)	20 (59) ⁴	6 (55)	4 (57)	14 (35)	17 (32)	

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²Excessive distal esophageal acid reflux is defined as distal esophageal acid reflux total time $\geq 4.2\%$ of 24-hour, or $\geq 6.3\%$ of upright position, or $\geq 1.2\%$ of supine position.

³ $P < 0.05$ for pharyngeal acid reflux alone *vs* both potential of hydrogen (-).

⁴ $P < 0.05$ for esophageal acid reflux alone *vs* both potential of hydrogen (-).

⁵ $P < 0.05$ for both potential of hydrogen (+) *vs* both potential of hydrogen (-).

⁶ $P < 0.05$ for pharyngeal acid reflux alone *vs* esophageal acid reflux alone.

⁷ $P < 0.05$ for pharyngeal acid reflux alone *vs* both potential of hydrogen (+).

⁸ $P < 0.05$ for esophageal acid reflux alone *vs* both potential of hydrogen (+).

PAR: Pharyngeal acid reflux; EAR: Esophageal acid reflux; pH: Potential of hydrogen; IQR: Interquartile range.