Name	Relevant employee experience	Relevant consultation experience	Personal ownership interest	Non-personal pecuniary interest	Relevant honorarium experience	Action required
Hve-Kvung Jung	None	None	None	None	None	None
Chung Hyun Tae	None	None	None	None	None	None
Kyung Ho Song	None	None	None	None	None	None
Seung Ioo Kang	None	None	None	None	None	None
Iong Kyu Park	None	None	None	None	None	None
Jong Eun Shin	None	None	None	None	None	None
Hvun Chul Lim	None	None	None	None	None	None
Sang Kil Lee	None	None	None	None	None	None
Da Hvun Jung	None	None	None	None	None	None
Yoon Iin Choi	None	None	None	None	None	None
Seung In Seo	None	None	None	None	None	None
Ioon Sung Kim	None	None	None	None	None	None
Jung Min Lee	None	None	None	None	None	None
Beom Iin Kim	None	None	None	None	None	None
Sun Hyung Kang	None	None	None	None	None	None
Chan Hyuk Park	None	None	None	Received research funding from Daewoong Pharmaceutical, Hanmi Pharmaceutical, and CI HealthCare	None	None
Suck Chei Choi	None	None	None	None	None	None
Joong Goo Kwon	None	None	None	Received research funding for ilapra- zole in NERD from IL-YANG PHARM, and tegoprazan in GERD from HK inno. N Corp	None	None
Kyung Sik Park	None	None	None	None	None	None
Moo In Park	None	None	None	None	None	None
Tae Hee Lee	None	None	None	None	None	None
Seung Young Kim	None	None	None	None	None	None
Young Sin Cho	None	None	None	None	None	None
Han Hong Lee	None	None	None	None	None	None
Eun Jeong Gong	None	None	None	None	None	None
Kee Wook Jung	None	None	None	Received research funding for tegoprazan from HK inno. N Corp	None	None
Do Hoon Kim	None	None	None	None	None	None
Hee Seok Moon	None	None	None	None	None	None
Hirota Miwa	None	None	None	Received research funding Pharmaceutical Co, Ltd, Otsuka Pharmaceutical Co, Ltd, Astra Zeneca Co, Ltd	Received honorarium from Takeda Pharmaceutical Co, Ltd, Otsuka Pharmaceutical Co, Ltd, Astra Zeneca Co, Ltd, Eisai Co, Ltd	None
Chien-Lin Chen	None	None	None	None	None	None
Sutep Gonlachanvit	None	None	None	None	Received lecturer's fees from Takeda Pharmaceutical Co, Ltd, and Otsuka Pharmaceutical Co, Ltd	None
Uday C Ghoshal	None	None	None	None	None	None
Justin C Wu	None	None	None	None	None	
Kewin T H Siah	None	None	None	None	None	None
Xiaohua Hou	None	None	None	None	None	None
Tadayuki Oshima	None	None	None	None	None	None
Mi-Young Choi	None	None	None	None	None	None
Kwang Jae Lee	None	None	None	None	None	None

Supplementary Table 1. Conflict of Interest Register

NERD, non-erosive reflux disease; GERD, gastroesophageal reflux disease.

Supplementary Table 2. Key Questions and Keywords Used in Meta-analyses

Key questions	Keywords
Is GERD increasing in Asia?	Gastroesophageal reflux, esophagitis, gastroesophageal, gastric acid, esophageal, GERD, GER, ERD, prevalence, epidemiology
Is a 2-week trial of a standard dose of PPI useful as a sensitive and practical test for GERD diagnosis in patients with typical GERD symptoms compared to 24-hour ambulatory pH-impedance monitoring?	Gastroesophageal reflux disease, erosive esophagitis, non-erosive esophagitis, a proton-pump inhibitor, omeprazole, esomeprazole, rabeprazole, pantoprazole, lansoprazole, ilaprazole, dexlansoprazole, wireless pH monitoring, impedance-pH monitoring, ambulatory reflux monitoring, pH monitoring, sensitivity, specificity
Is a double dose proton pump inhibitor effective for alleviating symptoms in patients with GERD who have insufficient effectiveness with standard proton pump inhibitors?	Proton pump inhibitor, PPI(s), acid suppression, acid suppression therapy, omeprazole, esomeprazole, rabeprazole, pantoprazole, lansoprazole, ilaprazole, dexlansoprazole, standard dose, high dose, double dose
Has on-demand PPI therapy more effective than continu- ous daily PPI therapy for the long-term management of patients with NERD or mild ERD?	Gastroesophageal reflux, esophagitis, heartburn, gastric acid reflux, esophageal reflux, GERD, GER, proton pump inhibitor, maintenance, recurrence, omeprazole, esomeprazole, rabeprazole, pantoprazole, lansoprazole, ilaprazole, dexlansoprazole, on-demand, on-demand, continuous, intermittent
Are proton pump inhibitors recommended to treat non-cardiac chest pain in patients with typical GERD symptoms?	Noncardiac chest pain, non-cardiac chest pain, atypical chest pain, functional chest pain, NCCP, proton pump inhibitor, proton pump inhibitors, omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, dexlansoprazole, ilaprazole, randomized controlled trial, controlled clinical trial, randomized, placebo, drug therapy, randomly, trial, groups
Are PPIs recommended for patients with Barrett's esophagus to reduce the risk of progression to high-grade dysplasia or adenocarcinoma?	Barrett, PPI, proton-pump inhibitor(s), proton pump inhibitor(s), omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, dexlansoprazole, ilaprazole, acid suppression, acid-suppressive, cancer(s), carcinoma(s), adenocarcinoma(s), dysplasia(s)
Are there potential risks associated with long-term proton pump inhibitor treatment?	Proton pump inhibitor, PPI(s), acid suppression, acid suppression therapy, omeprazole, esomeprazole, rabeprazole, pantoprazole, lansoprazole, ilaprazole, dexlansoprazole, clostridium difficile, clostridium infection, CDI, pseudomembranous colitis, <i>Clostridium difficile (C. difficile)</i> infection, <i>Clostridium difficile</i> (<i>C. difficile)</i> -associated diarrhea (CDAD), infection, diarrhea, colitis
Is the effect of P-CAB comparable with that of PPIs for the initial treatment of patients with GERD?	Potassium-competitive, P-CAB, vonoprazan, TAK-438, Takecab, tegoprazan, CJ12420, gastroesophageal reflux disease, GERD, nonerosive reflux disease, NERD, erosive re esophagitis, reflux
Does the combination of dose prokinetics with PPI improve GERD symptoms more than PPI monotherapy?	Gastroesophageal reflux disease, gastroesophageal reflux disease, gastroesophageal reflux, non-erosive reflux disease, reflux esophagitis, erosive reflux disease, endoscopy-negative reflux disease, proton pump inhibitor, prokinetic, prokinetics, erythromycin, metoclopramide, domperidone, cisapride, mosapride, itopride, ABT-229, alosetron, tegaserod, acotiamide, prucalopride, DA-9701, rikkunshito, promotility, relamorelin, cinitapride, ghrelin, revexepride, TZP-101, TZP-102

GERD, gastroesophageal reflux disease; GER, gastroesophageal reflux; ERD, erosive reflux disease; PPI, proton pump inhibitor; NERD, non-erosive reflux disease; NCCP, non-cardiac chest pain; CDI, *Clostridium difficile* infection; CDAD, *Clostridium difficile*-associated diarrhea; P-CAB, potassium competitive acid blocker.

First author	Year	Country	n	Mean AET (%)	ULN of AET (%)	Estimation method ^a
Yano et al ⁸⁹	2017	Japan	20	0.9	2.7	А
Netinatsunton et al ⁹⁰	2016	Thailand	34	0.5	1.9	А
Wu et al ⁹¹	2007	Hong Kong	28	0.2	0.6	А
Wu et al ⁹²	1999	China	20	1.3	3.5	А
Moon et al 93	2008	Korea	30	1.6^{b}	5.1	Bc
Ferdinandis et al ⁹⁴	2006	Sri Lanka	12	1.5^{b}	3.5	Bd
Ho and Kang ⁹⁵	2000	Singapore	15	1.9^{b}	4.0	Bd
Saraswat et al ⁹⁶	1994	India	16	1.7^{b}	3.0	Bd
Kim et al ⁹⁷	2008	Korea	50	1.3	4.0	С
Chun et al ⁹⁸	2000	Korea	25	1.4	3.6	Cc
Xiao et al ⁹⁹	2012	China	20	0.6^{b}	2.4	D
Ishimura et al ¹⁰⁰	2015	Japan	10	1.1	4.2	D
Kawamura et al ¹⁰¹	2016	Japan	42	NA	3.3	E
Wang et al ¹⁰²	2011	China	37	NA	3.1	Е
Xiao et al ¹⁰³	2009	China	70	NA	2.7	Е
Hu et al 104	2002	Hong Kong	20	NA	4.6	Е
Amarasiri et al ¹⁰⁵	2012	Sri Lanka	30	NA	1.5	Е
Yi et al ¹⁰⁶	2005	Taiwan	21	NA	7.0	Е
Kawamura et al ¹⁰⁷	2011	Japan	10	0.3	1.2	Fd

Supplementary Table 3. Asian Studies Included on the Meta-analyses of Acid Exposure Time in 24-Hour Ambulatory pH Monitoring

^aEstimation method: (A) if mean with standard deviation (SD) is present, upper limit of normal (ULN) is estimated by mean + 2SD, (B) if median (range) is present, mean and SD is calculated, and ULN is estimated with mean + 2SD, (C) if both mean with SD and median (range) are present, mean and SD is estimated by median (range) value, and ULN is estimated by mean + 2SD, (D) if median with interquartile range (IQR) is present, mean and SD is calculated, and ULN is estimated with mean + 2SD, (E) 95th percentile is present despite insufficiency of other data, ULN is determined as the presented 95th percentile, (F) if mean (range) is present, mean is used to calculate ULN, cif 95th percentile is present and is greater than estimated ULN using mean + 2SD, 95th percentile is used, and dif the maximum is present and is lower than estimated ULN using mean ± 2 SD, maximum is used.

AET, acid exposure time; ULN, upper limit of normal; NA, not applicable.

Reference	Study design	Number of patients	Mean BMI at baseline (kg/m ²)	Intervention	Follow-up duration	Outcome
De Bortoli et al, ¹⁴¹ 2016	Prospective open-label study	217	30.5 ± 4.0	Calorie-restricted diet (60% carbohydrate, 25% fat, and 15% protein) with aerobic exercise (weight loss of 10%) vs control	6 mo	Decreased symptom score Reduction or discontinuation of proton pump inhibitor
Singh et al, ¹³⁴ 2013	Prospective cohort study, single-arm	332	34.7 ± 4.6	Face-to-face or phone-based weight management program	6 mo	Improvement in reflux symptoms
Ness-Jensen et al, ¹⁴² 2013	Prospective population-based cohort study	29 610	26	No intervention		Dose-dependent symptom reduction and treatment success
Mathus-Vliegen and Tygat, ¹⁴³ 2002	Randomized controlled trials	34	43.4 ± 6.6	Intragastric balloon vs sham	65 wk	Improved reflux parameters
Fraser-Moodie, ¹⁴⁴ 1999	Prospective study, single-arm	34	23.5 ± 2.3	Dietary advice	26 wk	Decreased symptom score
Kjellin et al, ¹⁴⁵ 1996	Randomized controlled trials	20	31.4 (range 28-42)	Very low caloric diet for 6 weeks vs. control	6 mo	No improvement in reflux symptoms or objective measurements

Supplementary Table 4. Summary of the Evidence Supporting Weight Reduction in Patients With Gastroesophageal Reflux Disease

Data are presented as mean \pm SD.

Supplementary Table 5. Summary of Direct Comparison Trials Between the Efficacy of On-demand Proton Pump Inhibitor and Continuous Daily Proton Pump Inhibitor in the Long-term Management of Patients With Gastroesophageal Reflux Disease

Reference	Study design	Population	On-demand vs Continuous	Follow-up duration	Outcomes of the failure of PPI treatment
Jassen et al, ¹⁷¹	RCT	NERD and mild esophagitis treated with P 20 mg QD for 4 wk	P 20 mg vs P 20 mg	6 mo	Premature discontinuation due to insufficient symptom control
Hansen et al, ¹⁷⁰ 2005	RCT	Uninvestigated GERD received E 40 mg QD for 4 wk	E 20 mg vs E 20 mg	6 mo	Relapse is defined if they need a change in therapy, such as experiencing a relapse in symptoms
Sjöstedt et al, ¹⁶⁹ 2005	RCT	Investigated GERD (LA grades A-D), with endoscopically healed after E 40 mg QD for 4-8 wk	E 20 mg vs E 20 mg	6 mo	Relapse defined as if moderate or severe heartburn persisted for 3 consecutive days
Morgan et al, ¹⁶⁸ 2007	RCT	Minimum 3-month history of GERD who did on continuous daily PPI therapy for at least one month	R 20 mg vs R 20 mg	6 mo	Discontinuing for inadequate heartburn control
Szucs et al, ¹⁶⁷ 2009	RCT	Uninvestigated patients with GERD who demonstrated complete relief of symptoms after an initial treatment of 4 wk with E 40 mg	E 20 mg vs E 20 mg	26 wk	Relapse is defined as the "need for a change of therapy."
van der Velden et al, ¹⁶⁶ 2010	RCT	Continuous proton pump inhibitor or histamine-2-receptor antagonist) for > 6 mo	P 20 mg vs P 20 mg	13 wk	Discontinuing for inadequate relief and usage of rescue medication
Bayerdörffer et al, ¹⁶⁵ 2016	RCT	NERD who were heartburn-free after 4 wk' treatment with E 20 mg daily	E 20 mg vs E 20 mg	6 mo	Premature discontinuation due to unsatisfactory treatment

PPI, proton pump inhibitor; RCT, randomized controlled trial; NERD, non-erosive reflux disease; P, pantoprazole; E, esomeprazole; R, rabeprazole; QD, once a day; GERD, gastroesophageal reflux disease; LA, Los Angeles classification.





Study			ES (95% CI)
2010-2019			
Min (2014)	•		0.07 (0.06, 0.08)
Hung (2011)		-	0.25 (0.23, 0.28)
Tan (2016)			0.04 (0.03, 0.05)
Zhang (2019)	•		0.11 (0.10, 0.12)
Cai (2015)	•		0.05 (0.04, 0.06)
Niu (2012)		•	0.28 (0.26, 0.30)
Mungan (2012)	•	•	0.25 (0.24, 0.26)
Alsuwat (2018)	i T	*	0.29 (0.27 0.31)
Almadi (2014)		·	0.25 (0.27, 0.01) 0.45 (0.43, 0.48)
Darvishmoghadam (2016)		• ·	0.28 (0.26, 0.30)
Vossouchinia (2014)		*	0.20 (0.20, 0.30) 0.26 (0.24, 0.28)
Mansour-Chanaoi (2013)			0.20(0.24, 0.20) 0.12(0.10, 0.13)
Pourbosoingboli (2012)			
Koul (2012)	•		0.09(0.06, 0.09)
			0.20 (0.19, 0.22)
Wang (2016)	· · · · ·		0.22 (0.20, 0.25)
Bhatia (2011)	•		0.08 (0.07, 0.09)
Chong (2013)	- -		0.07 (0.05, 0.11)
Ghosh (2018)	•		0.07 (0.06, 0.08)
Shaha (2012)	•		0.05 (0.05, 0.07)
Abdullah (2016)	- + -i		0.09 (0.06, 0.13)
Subtotal ($I^{2} = 99.55\%, P = 0.00$)	$\langle -$		0.15 (0.11, 0.20)
2000-2009			
Lee (2009)			0.05 (0.04, 0.06)
Yang (2008)	•		0.11 (0.09, 0.13)
Cho (2005)	•		0.04 (0.03, 0.05)
Cheung (2007)	•		0.05 (0.04, 0.06)
Ma (2009)	♦		0.06 (0.05, 0.08)
Li (2008)	•		0.07 (0.07, 0.08)
Chen (2005)	•		0.03 (0.02, 0.03)
Wang (2004)	•		0.17 (0.16, 0.19)
Kitapçioğlu (2007)			0.20 (0.17, 0.23)
Sperber (2007)			0.09 (0.08, 0.11)
Mostaghni (2009)		-	0.33 (0.30, 0.37)
Solhpour (2008)	▲		0.09 (0.08, 0.10)
Nasseri-Moghaddam (2008)			0.18 (0.17, 0.20)
Nouraie (2007)			0.21 (0.20, 0.23)
Ehsani (2007)			0 15 (0 12 0 18)
Somi (2006)	T		0.06 (0.05, 0.08)
Lim (2005)			0.00(0.03, 0.00) 0.11(0.07, 0.15)
Subtotal ($I^2 = 98.93\%$, $P = 0.00$)			0.11 (0.08, 0.14)
Hataraganaity between groups: $P = 0.002$			
Overall ($l^2 = 99.42\%$, $P = 0.00$);	÷		0.13 (0.10, 0.16)
-1 -0.5	!	0.5	1
. 0.0	Prevalence	0.5	I

Supplementary Figure 2. Forest plot comparison of the prevalence of gastroesophageal reflux disease in population-based studies for 2 periods, 2000-2009 and 2010-2019. ES, effect size.



Supplementary Figure 3. Forest plot comparison of the prevalence of gastroesophageal reflux disease in observational studies of subjects who underwent medical check-ups in 2000-2009 and 2010-2019. ES, effect size.



Supplementary Figure 4. Forest plot comparison of non-erosive reflux disease prevalence in observational studies of subjects who underwent medical check-ups in 2000-2009 and 2010-2019. ES, effect size.



Supplementary Figure 5. Forest plot comparison of the prevalence of erosive reflux disease in observational studies of subjects who underwent medical check-ups in 2000-2009 and 2010-2019. ES, effect size.



Supplementary Figure 6. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram of the systematic review process of the diagnostic performance of empirical proton pump inhibitors in gastroesophageal reflux disease.



Supplementary Figure 7. Forest plot of sensitivity and specificity in a trial of proton pump inhibitors.



Univariable meta-regression and subgroup analyses

Supplementary Figure 8. Forest plot of subgroup analysis of dose (single versus double) and duration (< 2 weeks versus > 2 weeks) of proton pump inhibitors.



Supplementary Figure 9. Forest plot of upper limits of normal for the acid exposure time (AET [%]) in Asian studies.

	Experin	nental	Cont	rol		Risk ratio		Ri	isk ratio		
Study or subgroup	Events	Total	Events	Total	Weight	M-H, random, 95% CI	Year	M-H, ra	ndom, 95	% CI	
Orlando 2010	41	99	40	91	29.3%	0.94 [0.68, 1.31]	2010				
Chen 2010	62	100	41	110	33.1%	1.51 [1.14, 2.00]	2010				
Kinoshita 2012	80	111	53	110	37.6%	1.50 [1.19, 1.87]	2012		-		
Total (95% CI)		310		301	100.0%	1.31 [0.99, 1.73]			•		
Total events	183		134		0		L				
Heterogeneity: $Tau^2 =$	0.04; Chi ²	= 6.04,	df = 2 (P	P = 0.05); I ² = 67%	1	0.01	0.1	1	10	100
Test for overall effect:	Z = 1.91 ((P = 0.0)	6)				Favo	ors [experiment	tal] Favors	[control]

Supplementary Figure 10. Forest plot of symptom resolution in the double and standard dose proton pump inhibitor at 4 weeks in patients with gastroesophageal reflux disease. M-H, Mantel-Haenszel.

	Experin	nental	Cont	rol		Risk ratio		Ris	k ratio	
Study or subgroup	Events	Total	Events	Total	Weight	M-H, random, 95% CI	Year	M-H, ran	dom, 95% Cl	
Chen 2010	86	100	70	100	59.7%	1.23 [1.06, 1.43]	2010			
Kinoshita 2012	89	111	64	110	40.3%	1.38 [1.15, 1.66]	2012		-	
Total (95% CI)		211		210	100.0%	1.29 [1.15, 1.45]			•	
Total events	175		134		2		⊢			
Heterogeneity: $Tau^2 =$	0.00; Chi ²	= 0.93,	df = 1 (P)	P = 0.34		0.0	01 0.1	1 10	100	
Test for overall effect: 2	Z = 4.24 (P < 0.0	001)				Fav	vors [experimental] Favors [contr	ol]

Supplementary Figure 11. Forest plot of symptom resolution in the double and standard dose proton pump inhibitor at 8 weeks. M-H, Mantel-Haenszel.

	Experin	nental	Cont	rol		R isk ratio	Risk ratio
Study or subgroup	Events	Total	Events	Total	Weight	M-H, random, 95% CI	M-H, random, 95% CI
Armstrong 2004	485	772	686	1114	10.6%	1.02 [0.95, 1.10]	+
Bardhan 2007	137	214	129	204	6.3%	1.01 [0.88, 1.17]	+
Castell 2002	0	0	0	0		Not estimable	
Eggleston 2009	302	469	272	464	8.7%	1.10 [0.99, 1.22]	+
Fennerty 2005	344	478	307	483	9.5%	1.13 [1.04, 1.24]	-
Gilesen 2004	54	114	57	113	2.8%	0.94 [0.72, 1.23]	
Glatzel 2007	0	0	0	0		Not estimable	
Howden 2002	0	0	0	0		Not estimable	
Kahrilas 2000	402	621	357	624	9.4%	1.13 [1.03, 1.24]	-
Labenz 2005	1187	1562	1112	1589	12.3%	1.09 [1.04, 1.13]	•
Moraes-Filho 2014	165	270	170	278	6.9%	1.00 [0.87, 1.14]	+
Richter 2001	831	1216	702	1209	11.2%	1.18 [1.11, 1.25]	-
Schmitt 2006	374	576	361	572	9.6%	1.03 [0.94, 1.12]	+
Scholten 2003	103	105	111	112	12.7%	0.99 [0.96, 1.02]	
Zheng 2009	0	0	0	0		Not estimable	
Total (95% CI)		6397		6762	100.0%	1.06 [1.01, 1.12]	
Total events	4384		4264		2		I I I I I I I I I I I I I I I I I I I
Heterogeneity: Tau ² =	0.00; Chi ²	= 48.29,	df = 10 (P	P < 0.000	$(001); I^2 = 79$	9%	0.01 0.1 1 10 100
Test for overall effect:	Z = 2.44 (<i>F</i>	P = 0.01					Favors [experimental] Favors [control]

Supplementary Figure 12. Forest plot of symptom relief in subjects on esomeprazole 40 mg per day and other standard dose proton pump inhibitors at 4 weeks. M-H, Mantel-Haenszel.

	Experin	nental	Cont	trol		R isk ratio	Risk ratio
Study or subgroup	Events	Total	Events	Total	Weight	M-H, random, 95% CI	M-H, random, 95% Cl
Armstrong 2004	0	0	0	0		Not estimable	
Bardhan 2007	243	293	248	288	8.0%	0.96 [0.90, 1.03]	-
Castell 2002	0	0	0	0		Not estimable	
Eggleston 2009	0	0	0	0		Not estimable	
Fennerty 2005	410	498	388	501	8.9%	1.06 [1.00, 1.13]	+
Gilesen 2004	70	76	69	77	5.2%	1.03 [0.93, 1.14]	+
Glatzel 2007	0	0	0	0		Not estimable	
Howden 2002	123	138	127	139	7.2%	0.98 [0.90, 1.05]	4
Kahrilas 2000	615	654	565	650	12.7%	1.08 [1.04, 1.12]	•
Labenz 2005	1431	1562	1413	1589	14.4%	1.03 [1.01, 1.05]	+
Moraes-Filho 2014	253	279	246	284	9.3%	1.05 [0.99, 1.11]	+
Richter 2001	1139	1216	1018	1209	13.7%	1.11 [1.08, 1.14]	•
Schmitt 2006	531	576	514	572	12.6%	1.03 [0.99, 1.06]	+
Scholten 2003	0	0	0	0		Not estimable	
Zheng 2009	62	65	178	199	7.8%	1.07 [0.99, 1.15]	+
Total (95% CI)		5357		5508	100.0%	1.04 [1.02, 1.07]	
Total events	4877		4766		0		
Heterogeneity: Tau ² =	0.00; Chi ⁻	= 32.49,	df = 9 (<i>P</i>	= 0.0002	2); l ⁻ = 72%		0.01 0.1 1 10 100
Test for overall effect:	Z = 3.04 (#	P = 0.002	2)				Favors [experimental] Favors [control]

Supplementary Figure 13. Forest plot of symptom relief in subjects on esomeprazole 40 mg per day and other standard dose proton pump inhibitors at 8 weeks. M-H, Mantel-Haenszel.

	On dema	und PPI	Continuo	ous PP	I	R isk ratio			Risk	ratio	
Study or subgroup	Events	Total	Events	Total	Weight	M-H, random, 95% Cl	Year		M-H, rand	om, 95% Cl	
Sjostedt 2005	49	234	12	243	15.1%	4.24 [2.32, 7.77]	2005				
Hansen 2005	69	634	46	658	17.8%	1.56 [1.09, 2.22]	2005				
Janssen 2005	13	215	17	217	14.0%	0.77 [0.38, 1.55]	2005			<u> </u>	
Morgan 2007	6	131	3	137	7.7%	2.09 [0.53, 8.19]	2007				
Szucs 2009	60	991	55	913	17.8%	1.01 [0.70, 1.43]	2009			-	
van der Velden 2010	34	141	5	62	11.9%	2.99 [1.23, 7.28]	2010			_	
Bayerdorffer 2016	19	301	29	297	15.7%	0.65 [0.37, 1.13]	2016			ł	
Total (95% CI)		2647		2527	100.0%	1.46 [0.90, 2.38]					
Total events	250		167						1	-	
Heterogeneity: Tau ² =	= 0.31; Chi ^ź	² = 29.86	6, df = 6 (P)	< 0.00	01); $I^2 = 80$	%		0.01	0.1	1 10	100
Test for overall effect	: Z = 1.53 (P = 0.13	3)					Favo	rs on-demand	Favors conti	nuous

Supplementary Figure 14. Forest plot of risk ratios of failure between on-demand proton pump inhibitor (PPI) and continuous PPI groups in long-term management. M-H, Mantel-Haenszel.

	On dema	nd PPI	Continuo	ous PP	1	R isk ratio		Risk ratio
Study or subgroup	Events	Total	Events	Total	Weight	M-H, random, 95% Cl	Year	M-H, random, 95% Cl
6.1.1. Symptomatic G	GERD							
Hansen 2005	69	634	46	658	17.8%	1.56 [1.09, 2.22]	2005	
Morgan 2007	6	131	3	137	7.7%	2.09 [0.53, 8.19]	2007	
Szucs 2009	60	991	55	913	17.8%	1.01 [0.70, 1.43]	2009	+
Subtotal (95% CI)		1756		1708	43.3%	1.29 [0.89, 1.87]		•
Total events	135		104			- , -		Ť
Heterogeneity: $Tau^2 =$	0.04; Chi ²	= 3.44, 0	df = 2 (<i>P</i> =	: 0.18);	$l^2 = 42\%$			
Test for overall effect:	Z = 1.37 (P = 0.17)					
6.1.2 NERD only								
Bayerdorffer 2016	19	301	29	297	15.7%	0.65 [0.37, 1.13]	2006	
Subtotal (95% CI)		301		297	15.7%	0.65 [0.37, 1.13]		•
Total events	19		29					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 1.54 (<i>l</i>	P = 0.12)					
6.1.3 NERD and mild	EE							
Janssen 2005	13	215	17	217	14.0%	0.77 [0.38, 1.55]	2005	
Van der Velden 2010	34	141	5	62	11.9%	2.99 [1.23, 7.28]	2010	
Subtotal (95% CI)		356		279	25.9%	1.48 [0.39, 5.63]		
Total events	47		22					
Heterogeneity: $Tau^2 =$	0.77; Chi ²	= 5.62, 0	df = 1 (<i>P</i> =	: 0.02);	$l^2 = 82\%$			
Test for overall effect:	Z = 0.57 (P = 0.57)					
Sigstadt 2005	10	234	10	2/3	15 1%	1 94 [9 39 7 77]	2005	
Subtotal (95% CI)	40	234	12	240	15 1%	A 24 [2:02, 7:77]	2005	
Total events	10	204	12	240	13.170	4.24 [2.02, 1.11]		
Heterogeneity: Not an	nlicable		12					
Test for overall effect:	Z = 4.68 (/	P < 0.00	001)					
					400.004			
Iotal (95% CI)	050	2647	4.07	2527	100.0%	1.46 [0.90, 2.38]		•
Iotal events	250	00.00	167		$a u^2 \alpha$	20/	ŀ	
Heterogeneity: lau =	0.31; Chi	= 29.86	at = 6 (P)	< 0.000	(1); I = 80	J%	(0.01 0.1 1 10 100
lest for overall effect:	$\angle = 1.53$ (/	P = 0.13)		2 a a a a a a	0= 10/		Favors on-demand Favors continuous
Test for subgroup diff	erences: C	nı = 20	.48, $dt = 3$	(P = 0.	UUU1), i =	= 85.4%		

Supplementary Figure 15. Forest plot of risk ratios of failure between on-demand proton pump inhibitor (PPI) and continuous PPI groups in long-term management according to each subgroup analysis. GERD, gastroesophageal reflux disease; NERD, non-erosive reflux disease; EE, erosive esophagitis. M-H, Mantel-Haenszel.

	On dema	und PPI	Continuo	ous PP	I	R isk ratio			F	Risk ratio	atio			
Study or subgroup	Events	Total	Events	Total	Weight	M-H, random, 95% CI	Year		M-H, r	andom, 9	95% CI			
Sjostedt 2005	225	234	241	243	25.6%	0.97 [0.94, 1.00]	2005							
Hansen 2005	478	634	541	658	19.8%	0.92 [0.87, 0.97]	2005							
Morgan 2007	104	131	126	137	12.1%	0.86 [0.78, 0.95]	2007			-				
Szucs 2009	932	991	849	913	26.3%	1.01 [0.99, 1.04]	2009			•				
Bayerdorffer 2016	246	301	246	297	16.3%	0.99 [0.92, 1.06]	2016			+				
Total (95% CI)		2291		2248	100.0%	0.96 [0.92, 1.00]								
Total events	1985		2003					L						
Heterogeneity: Tau ² = 0.00; Chi ² = 21.18, df = 4 (P = 0.0003); I ² = 819						%		0.01	0.1	1	10	100		
Test for overall effect:	Z = 1.79 (P = 0.07)					Fav	ors continu	ious Favo	rs on-dem	and		

Supplementary Figure 16. Forest plot of the satisfaction between the on-demand proton pump inhibitor (PPI) and continuous PPI groups in long-term management. M-H, Mantel-Haenszel.

	On de	On demand PPI Continuous PPI					Mean difference				Mean difference				
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, random, 9	5% CI	Year		IV, ra	ndon	n, 95% CI	
Janssen 2005	0.51	0.31	215	0.93	0.17	217	47.8%	-0.42 [-0.47,	-0.37]	2005					
Bayerdorffer 2016	0.41	0.25	301	0.91	0.16	297	52.2%	-0.50 [-0.53,	-0.47]	2016			•		
Total (95% CI)	- 0 00. C	`hi ² —	516	f — 1 (P	- 0.0	514	100.0%	-0.46 [-0.54,	-0.38]						
Test for overall effect	: Z = 11	.56 (P	< 0.00	0001)	- 0.0	,07), 1	- 0070				-100 Favors [e	-50 experimer	0 ntal] I	50 Favors [con	100 trol]

Supplementary Figure 17. Forest plot of medication use between on-demand proton pump inhibitor (PPI) and continuous PPI groups in long-term management.

	PF	PI	Placebo			Odds ratio)			
Study or subgroup	Events	Total	Events	Total	Weight	M-H, fixed, 95% CI		М-Н,	fixed, 95	% CI	
Achem 1997	7	16	3	18	5.7%	3.89 [0.80, 18.97]					
Bautista 2004	14	18	4	18	3.2%	12.25 [2.54, 58.97]			-	•	
Dickman 2005	12	16	3	16	2.7%	13.00 [2.40, 70.46]			_		
Fass 1998	18	23	6	23	4.7%	10.20 [2.62, 39.72]			-		
Flook 2013	55	142	39	153	83.2%	1.85 [1.13, 3.04]					
Pandek 2002	18	20	1	20	0.4%	171.00 [14.24, 2053.25]					
Total (95% CI)		235		248	100.0%	3.61 [2.46, 5.29]					
Total events	124		56				L				
Heterogeneity: $Chi^2 = 23$	0.03, df = 5 (P = 0.00	$(03); I^2 = 7$	8%			0.01	0.1	1	10	100
Test for overall effect: Z	= 6.56 (<i>P</i> <	0.00001)						Deteriora	tion Impr	ovement	

Supplementary Figure 18. Forest plot of the benefits from the proton pump inhibitor (PPI) treatment in gastroesophageal reflux disease positive patients with non-cardiac chest pain. M-H, Mantel-Haenszel.

	PP	21	Placebo			Risk ratio	Risk ratio				
Study or subgroup	Events	Total	Events	Total	Weight	M-H, fixed, 95% CI		М-Н,	fixed, 95	% CI	
Achem 1997	0	0	0	0		Not estimable					
Bautista 2004	2	22	8	22	16.5%	0.25 [0.06, 1.05]					
Dickman 2005	2	19	4	19	8.3%	0.50 [0.10, 2.41]					
Fass 1998	2	14	1	14	2.1%	2.00 [0.20, 19.62]					
Flook 2013	37	136	32	132	67.0%	1.12 [0.75, 1.69]			-		
Pandek 2002	6	18	3	18	6.2%	2.00 [0.59, 6.79]					
Total (95% CI)		209		205	100.0%	1.00 [0.70, 1.42]			•		
Total events	49		48				—				
Heterogeneity: $Chi^2 = 6.2$	24, df = 4 (P)	= 0.18);	$I^2 = 36\%$				0.01	0.1	1	10	100
Test for overall effect: Z =	= 0.00 (<i>P</i> =	1.00)						Deteriora	tion Impr	ovement	

Supplementary Figure 19. Forest plot of the benefits from the proton pump inhibitor (PPI) treatment in gastroesophageal reflux disease negative patients with non-cardiac chest pain. M-H, Mantel-Haenszel.



Supplementary Figure 20. Forest plot of the odds ratio of proton pump inhibitor (PPI) medication in the risk of progression into high-grade dysplasia or adenocarcinoma.

Study or subgroup	Log [odds ratio]	SE	Weight	Odds ratio IV, random, 95% CI		IV, ra	Odds ratio andom, 95%	% CI	
Beaulieu 2007	0.3293	0.1996	7.4%	1.39 [0.94, 2.06]			_ _		
Dalton 2009	0.6729	0.1644	7.7%	1.96 [1.42, 2.71]			_ _		
Dial 2004	0.7419	0.2736	6.6%	2.10 [1.23, 3.59]			_	-	
Dubberke 2007	0.6831	0.2772	6.6%	1.98 [1.15, 3.41]				-	
Faleck 2016	-0.4463	0.1448	7.9%	0.64 [0.48, 0.85]					
Howell 2010	0.5539	0.1146	8.1%	1.74 [1.39, 2.18]					
Ingle 2011	0.6098	0.7185	2.9%	1.84 [0.45, 7.52]					
Khan 2012	1.1694	0.4994	4.3%	3.22 [1.21, 8.57]					
Khanafer 2013	0.9361	0.6819	3.1%	2.55 [0.67, 9.70]					
Lewis 2016	1.8656	0.2941	6.4%	6.46 [3.63, 11.50]				_ _	
Loo 2011	0.9708	0.2216	7.2%	2.64 [1.71, 4.08]				_	
Peled 2007	1.3244	0.4621	4.7%	3.76 [1.52, 9.30]			—	•	
Pepin 2005	0	0.1203	8.1%	1.00 [0.79, 1.27]			+		
Ro 2016	1.1939	0.4023	5.2%	3.30 [1.50, 7.26]					
Roughead 2016	0.8755	0.1192	8.1%	2.40 [1.90, 3.03]					
Southern 2010	0.8416	0.3449	5.8%	2.32 [1.18, 4.56]					
Total (95% CI)			100.0%	2.03 [1.52, 2.72]			•		
Heterogeneity: $Tau^2 =$	0.26; Chi ² = 108.62, df	= 15 (P <	0.00001);	$l^2 = 86\%$	L			1	
Test for overall effect:	$Z = 4.77 \ (P < 0.00001)$				0.01	0.1	1	10	100
					F=	ivors lexperime	entall Favors	s [control]	100
					10	cons lexberning	intaij i avoit	loontiol	

Supplementary Figure 21. Forest plot of the odds ratio of proton pump inhibitor medication in the risk of Clostridium difficile infection.

	P-CAB		PPI			Risk ratio	Ris	k ratio	
Study or subgroup	Events	Total	Events	Total	Weight	M-H, fixed, 95% Cl	M-H, fix	ed, 95% Cl	
Ashida 2015	139	144	126	132	21.0%	1.01 [0.96, 1.06]		•	
Ashida 2016	203	205	190	199	30.8%	1.04 [1.00, 1.07]		•	
Lee 2018	91	92	87	88	14.2%	1.00 [0.97, 1.03]		+	
Xiao 2019	220	238	210	230	34.1%	1.01 [0.96, 1.07]		•	
Total (95% CI)		679		649	100.0%	1.02 [0.99, 1.04]			
Total events	653		613				L		
Heterogeneity: $Chi^2 = 2.5$	53, df = 3 (<i>P</i>	= 0.47);	$l^2 = 0\%$				0.01 0.1	1 10	100
Test for overall effect: Z =	= 1.48 (<i>P</i> =	0.14)					Favors [experimental] Favors [contro]

Supplementary Figure 22. Forest plot of the risk ratio of potassium-competitive acid blockers (P-CABs) in erosive esophagitis healing rates at 8 weeks. PPI, proton pump inhibitor. M-H, Mantel-Haenszel.

	PPI + prokinetics PPI					R isk ratio	Ris	k ratio
Study or subgroup	Events	Total	Events	Total	Weight	M-H, random, 95% Cl	M-H, rand	iom, 95% Cl
2.1.1 PPI + mosapride v	s PPI							
Cho 2013	19	24	13	19	6.8%	1.16 [0.80, 1.67]		
Hsu 2010	39	44	41	50	24.1%	1.08 [0.91, 1.28]		+
Lee 2017	46	60	36	56	14.2%	1.19 [0.94, 1.52]		
Madan 2004	25	28	23	33	12.5%	1.28 [0.99, 1.66]		+=-
Miwa 2011	45	97	42	95	9.1%	1.05 [0.77, 1.43]		- - -
Wang 2014	48	58	38	58	16.2%	1.26 [1.01, 1.57]		-
Subtotal (95% CI)		311		311	82.9 %	1.16 [1.05, 1.28]		•
Total events	222		193					
Heterogeneity: $Tau^2 = 0.0$)0; Chi ² = 2	.27, df =	= 5 (P = 0)).81); l ² :	= 0%			
Test for overall effect: Z =	= 3.02 (<i>P</i> =	0.002)						
2.1.2 PPI + other prokin	etics vs P	PI						
Marakhouski 2017	25	50	13	50	3.3%	1.92 [1.12, 3.31]		
Shaheen 2015	71	118	51	122	12.8%	1.44 [1.11, 1.86]		
Yamashita 2019	10	35	5	35	1.1%	2.00 [0.76, 5.25]		+
Subtotal (95% CI)		203		207	17.1%	1.54 [1.23, 1.93]		•
Total events	106		69	0				
Heterogeneity: $Tau^2 = 0.0$)0; Chi [∠] = 1	.23, df =	= 2 (P = 0)).54); lÉ	= 0%			
Test for overall effect: Z =	= 3.76 (<i>P</i> =	0.0002)						
Total (95% CI)		514		518	100.0%	1.22 [1.11, 1.35]		
Total events	328	••••	262	010	1001070			
Heterogeneity: $Tau^2 = 0.0$	$10 \cdot \text{Chi}^2 = 9$	46 df =	= 8 (P = 0)	$(31) \cdot 1^2$	= 15%		0.01 0.1	
Test for overall effect: 7 =	= 3 94 (P <	0.0001)	0,0 - 0		1070			I IV IVU
Test fan auk and differen	chi^2	E 00	If _ 1 (D	0.001	$1^2 - 20, 20$	/	Favors [PPI	j ravois [rri + prokinetics]

Supplementary Figure 23. Forest plot of the risk ratio of proton pump inhibitor (PPI) plus prokinetics treatment in reducing global symptoms of gastroesophageal reflux disease. M-H, Mantel-Haenszel.

	PPI + pro	2		Risk ratio		Risk ratio					
Study or subgroup	Events	Total	Events	Total	Weight	M-H, random, 95% Cl		M-H, random, 95% CI			
Studies only included	patients wi	th refra	ctory GE	RD							
Shaheen 2015	71	118	51	122	12.8%	1.44 [1.11, 1.86]					
Yamashita 2019	10	35	5	35	1.1%	2.00 [0.76, 5.25]					
Subtotal (95% CI)		153		157	13.8%	1.47 [1.15, 1.88]			•		
Total events	81		56								
Heterogeneity: $Tau^2 = 0$.	00; $Chi^2 = 0$).43, df =	= 1 (<i>P</i> = 0	.51); I ² =	= 0%		0.01	0.1	1	10	100
Test for overall effect: Z	= 3.06 (<i>P</i> =	0.002)						Favors	PPI] Favor	s [PPI + I	prokinetics]

Supplementary Figure 24. Forest plot of the risk ratio of proton pump inhibitor (PPI) plus prokinetics treatment in reducing global symptoms of refractory gastroesophageal reflux disease. M-H, Mantel-Haenszel.