Anti-reflux Therapy in IPF cons

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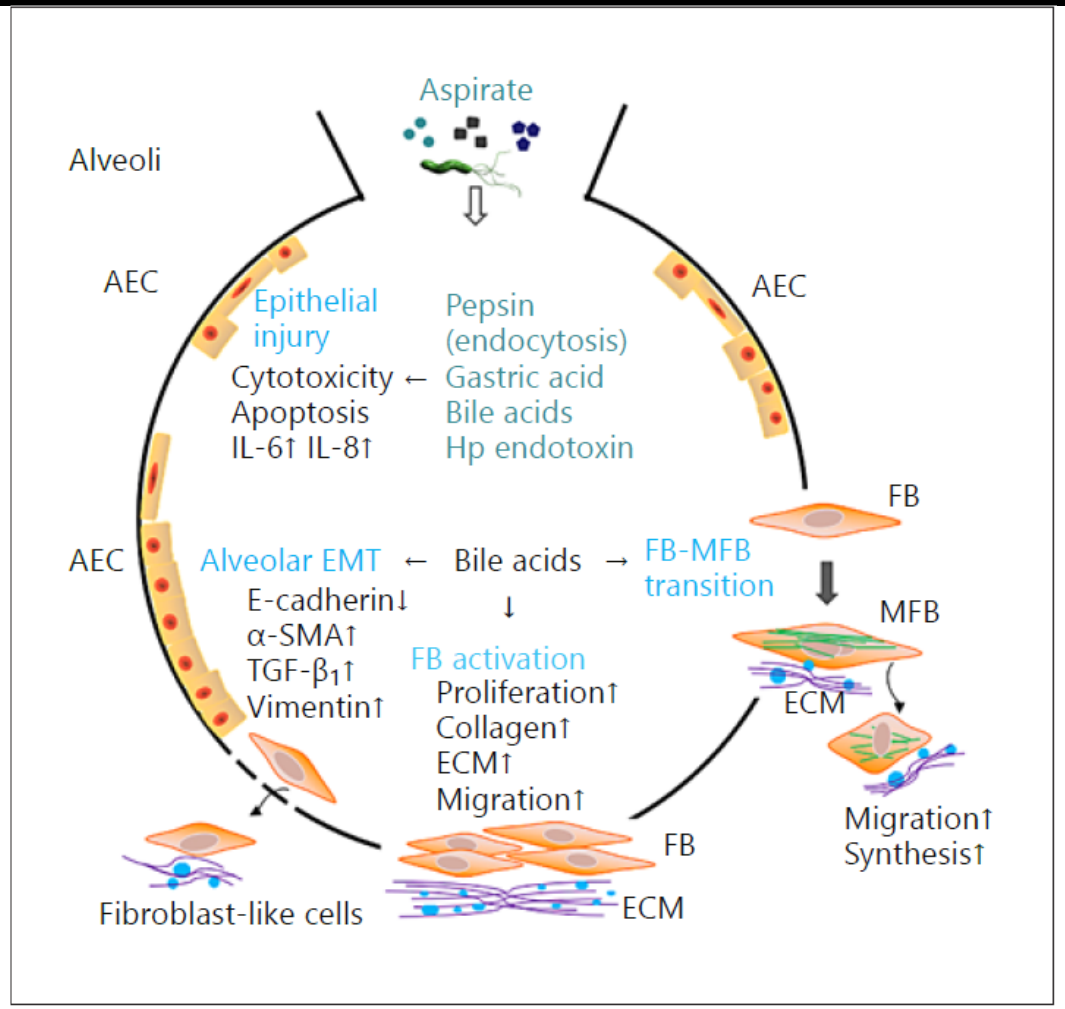
Association between GERD and IPF

- GERD, its prevalence seems to be significantly high in patients with IPF
- The prevalence and risk of pulmonary fibrosis was higher in patients with GERD (case-control study)
- Detection of gastric contents (acids and pepsin) with lower pH in the BALF of patients with IPF
- Chronic aspiration (GERD) induces interstitial pneumonitis and lung fibrosis, in Cellular and animal models
- Airway-centered fibroblast foci in the lungs of some patients with IPF – consistent with chronic aspiration-induced lung pathology

The possible mechanisms of pulmonary fibrosis induced by microaspiration



Factors that may worsen GERD in IPF

Lung mechanics

- Decreased lung compliance
- Altered intrathoracic pressure
- Hiatal hernia
- Mediastinal distortion

Drugs

- Corticosteroids
- Pirfenidone

Complications and comorbidities

- Respiratory failure
- Airway hyperresponsiveness
- Anxiety/depression
- OSAHS, obstructive sleep apnea-hypopnea syndrome

Comparison of Recommendations in the 2015 and 2011 IPF Guidelines

Agent	2015 Guideline	2011 Guideline
New and revised recommendations		
Anticoagulation (warfarin)	Strong recommendation against use*	Conditional recommendation against use‡
Combination prednisone + azathioprine + *N*-acetylcysteine	Strong recommendation against use†	Conditional recommendation against use†
Selective endothelin receptor antagonist (ambrisentan)	Strong recommendation against use†	Not addressed
Imatinib, a tyrosine kinase inhibitor with one target	Strong recommendation against use*	Not addressed
Nintedanib, a tyrosine kinase inhibitor with multiple targets	Conditional recommendation for use*	Not addressed
Pirfenidone	Conditional recommendation for use*	Conditional recommendation against use†
Dual endothelin receptor antagonists (macitentan, bosentan)	Conditional recommendation against use†	Strong recommendation against use*
Phosphodiesterase-5 inhibitor (Sildenafil)	Conditional recommendation against use*	Not addressed
Unchanged recommendations		
Antiacid therapy	Conditional recommendation for use‡	Conditional recommendation for use‡
N-acetylcysteine monotherapy	Conditional recommendation against use†	Conditional recommendation against use†
Antipulmonary hypertension therapy for idiopathic pulmonary fibrosis-associated pulmonary hypertension	Reassessment of the previous recommendation was deferred	Conditional recommendation against use‡
Lung transplantation: single vs. bilateral lung transplantation	Formulation of a recommendation for single vs. bilateral lung transplantation was deferred	Not addressed

*⊕⊕⊕⊖, moderate confidence in effect estimates.
†⊕⊕⊖⊖, low confidence in effect estimates.
‡⊕⊖⊖⊖, very low confidence in effect estimates.

The problem

- The guideline recommendation for antacid therapy and 2 antifibrotic drugs pirfenidone and Nintedanib
  - **same conditional recommendations for use**

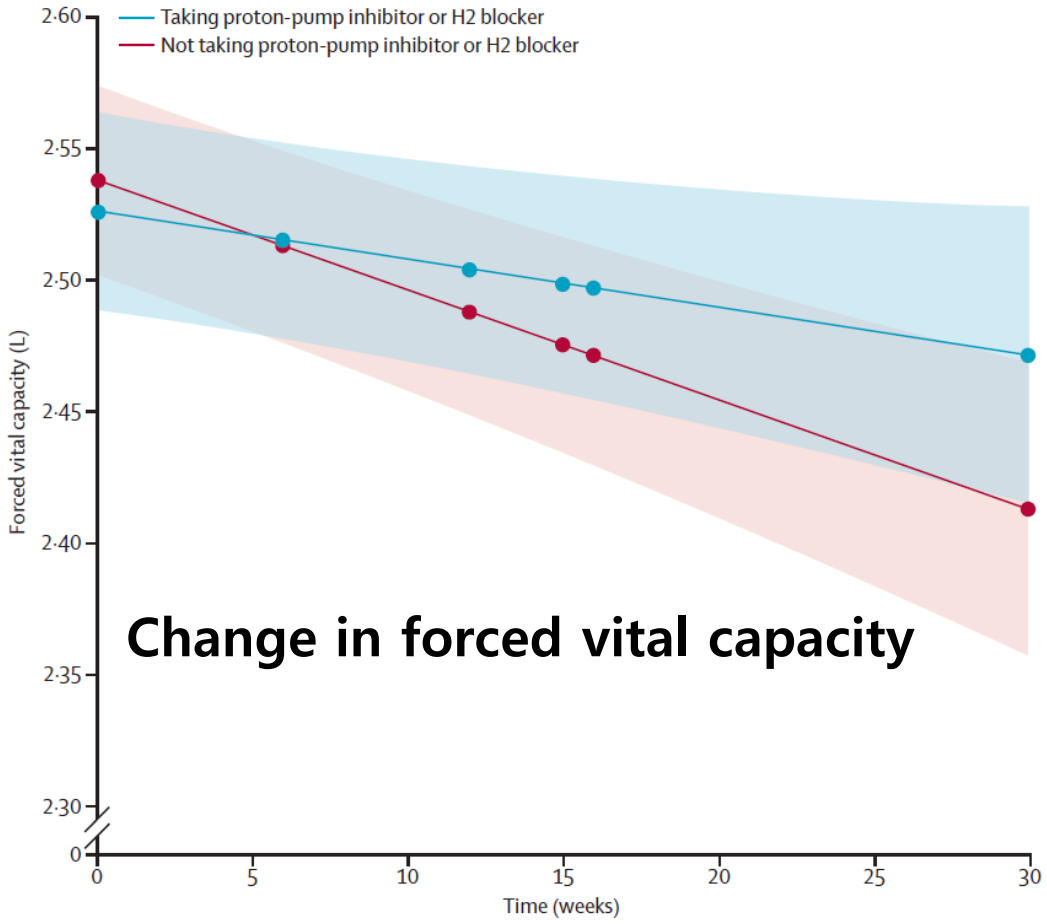
- Are there same strong evidences for antacid therapy as 2 antifibrotic drugs?
  - No Randomized controlled studies focused on antacid therapy

Anti-acid treatment and disease progression in IPF
: an analysis of data from three randomized controlled trials

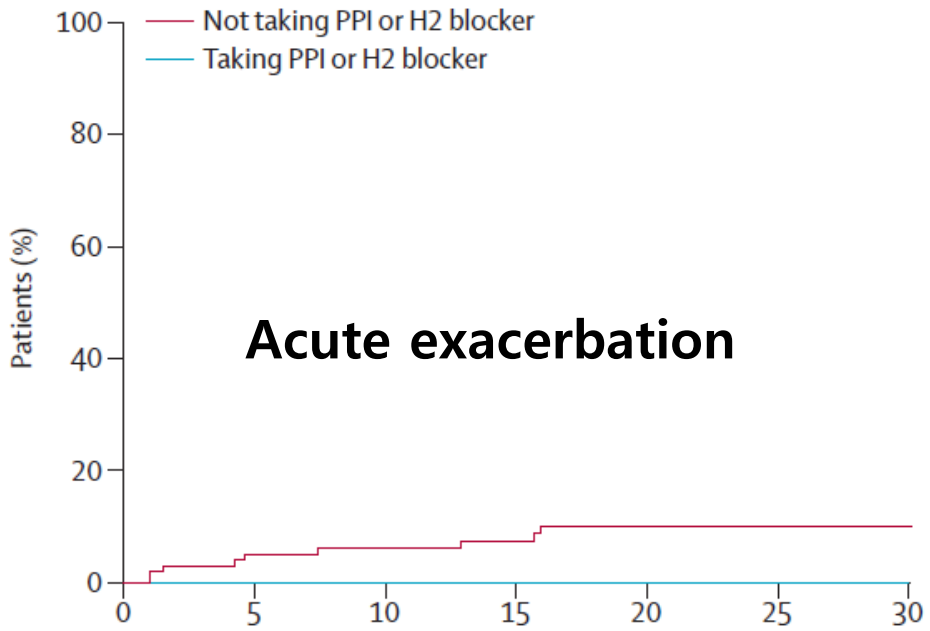
- 242 patients (124, 51% patients with anti-acid treatment) randomly assigned to the placebo groups of the three trials
  - **STEP-IPF (N=180, Sildenafil Trial)**
  - **ACE-IPF (N=145, for Anticoagulant Effectiveness)**
  - **PANTHER-IPF (N=155, Prednisone, Azathioprine, and N-Acetylcysteine)**
- Change in FVC at 30 weeks (mean follow-up)

Lancet Respir Med 2013;1: 369–76

	Change in 30 weeks (L)		
	Taking PPI or H2 blocker	**Not taking PPI or H2 blocker**	**P value**
Overall	–0·06 (–0·11 to –0·01)	–0·12 (–0·17 to –0·08)	**0·05**
Estimated change in 52 weeks	–0·09 (–0·18 to –0·01)	–0·21 (–0·29 to –0·13)	**0·04**
30-week estimate with data only from <30 weeks after enrolment	–0·10 (–0·18 to –0·03)	–0·17 (–0·23 to –0·10)	**0·19**
With adjustment for study	–0·05 (–0·10 to 0·00)	–0·12 (–0·17 to –0·08)	**0·05**
Exclusion of patients taking H2 blockers	–0·05 (–0·10 to 0·00)	–0·12 (–0·17 to –0·08)	**0·05**
Exclusion of patients with acute exacerbations	–0·05 (–0·11 to 0·00)	–0·12 (–0·17 to –0·08)	**0·05**
Exclusion of patients who stopped or started taking PPI or H2 blockers during study	–0·05 (–0·10 to 0·00)	–0·12 (–0·17 to –0·08)	**0·05**
With adjustment for treatment of sleep apnoea	–0·06 (–0·11 to –0·01)	–0·12 (–0·17 to –0·08)	**0·05**



Change in forced vital capacity



Acute exacerbation

Number at risk							
Not taking PPI or H2 blocker	118	102	99	82	75	70	33
Taking PPI or H2 blocker	124	115	112	100	91	85	52

What we should consider in the study

- No detailed information of anti-acid treatment (treatment duration, objective diagnostic test …)
- Very small effect in view of FVC measurement (estimated difference 0·07 L, 95% CI 0–0·14; p=0·05)
- No available effective anifibrotics at the time of the study

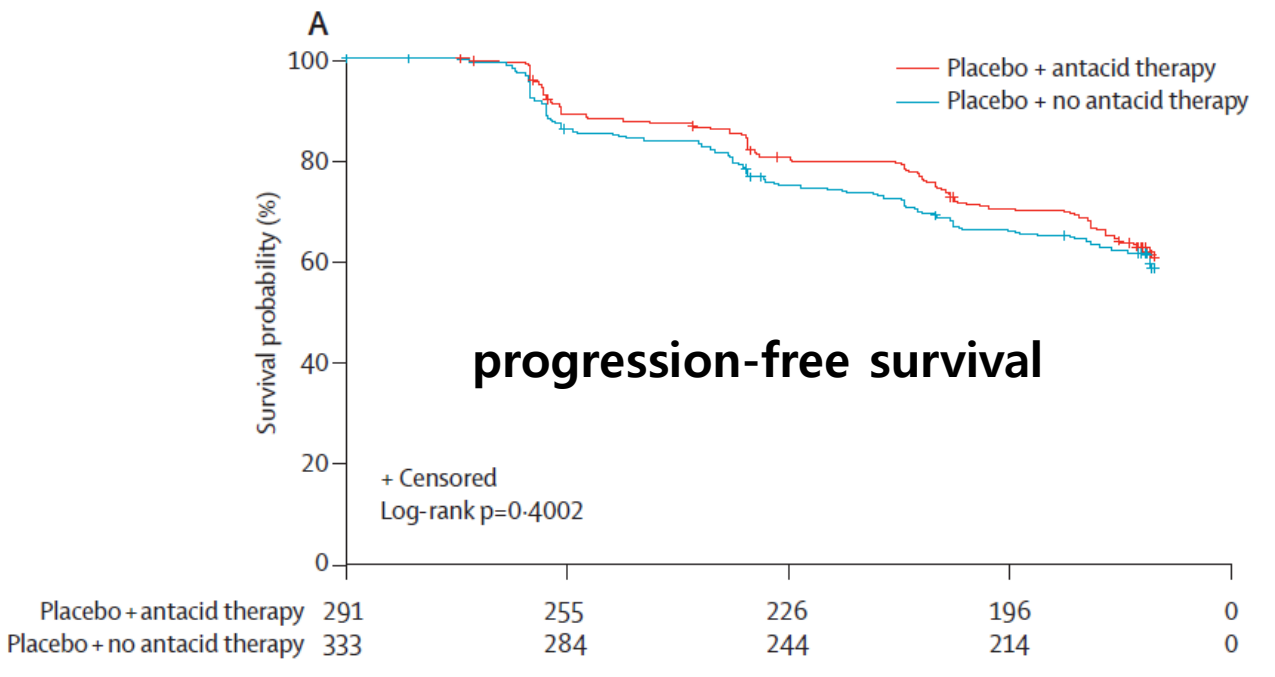
Antacid therapy and disease outcomes in IPF : a pooled analysis

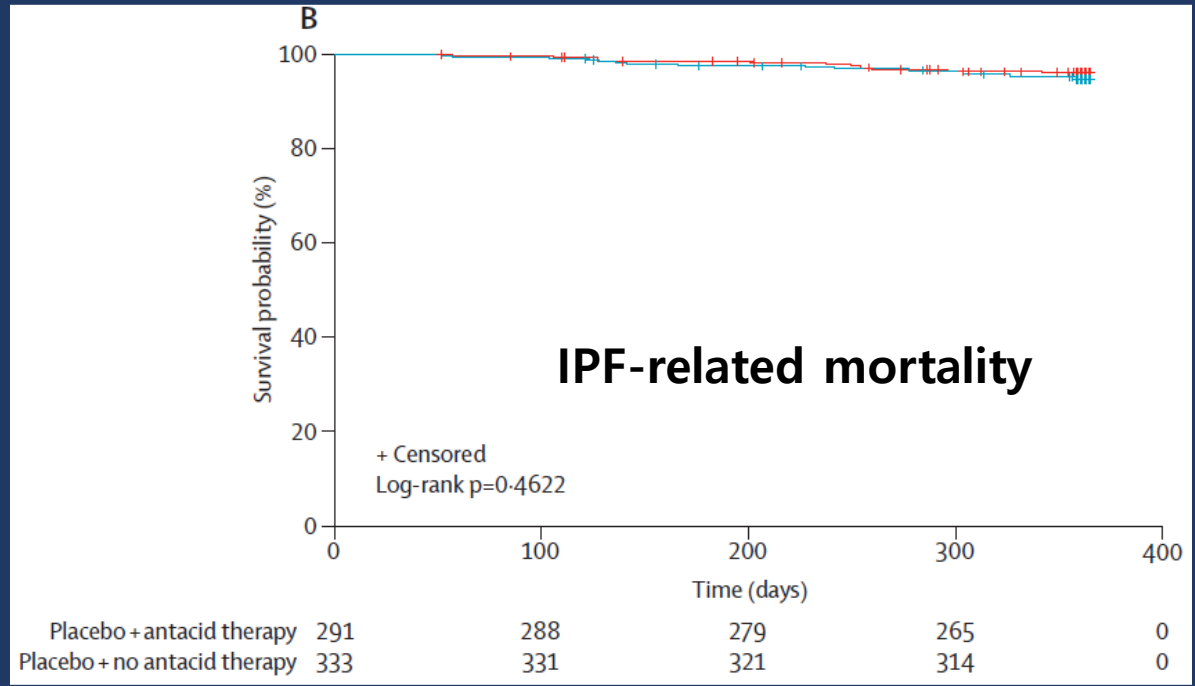
- Patients with IPF from the placebo groups of three trials of pirfenidone **(CAPACITY 004, CAPACITY 006, and ASCEND)**

- Aimed to investigate the effect of antacid therapy on disease progression

Lancet Respir Med 2016; 4: 381–89

	Antacid therapy* (N=291)	No antacid therapy* (N=333)	p value
Disease progression†			
Any‡	114 (39%)	141 (42%)	0·4844
All-cause mortality	14 (5%)	18 (5%)	0·7370
FVC decrease (absolute) ≥10%§	32 (11%)	37 (11%)	0·9637
6MWD decrease ≥50 m§	68 (23%)	86 (26%)	0·4774
Mortality			
All-cause	20 (7%)	22 (7%)	0·8947
IPF-related	11 (4%)	17 (5%)	0·4251
FVC change			
FVC change (observed; % predicted)	–4·9 (6·4)	–5·5 (7·2)	0·3355
FVC change (imputed; % predicted)	–9·3 (16·7)	–9·4 (16·6)	0·8951
FVC change (observed; L)	–0·2 (0·3)	–0·2 (0·3)	0·4238
Other outcomes			
6MWD decrease ≥50 m¶	72 (25%)	94 (28%)	0·3256
All-cause hospital admission	65 (22%)	54 (16%)	0·0522
Side-effects			
Gastrointestinal side-effects	166 (57%)	174 (52%)	0·2304
Infections	201 (69%)	217 (65%)	0·3005
Pulmonary infections	27 (9%)	20 (6%)	0·1223


A
Placebo + antacid therapy
Placebo + no antacid therapy
Survival probability (%)
100
80
60
40
20
0
progression-free survival
+ Censored
Log-rank p=0·4002
Placebo + antacid therapy 291 255 226 196 0
Placebo + no antacid therapy 333 284 244 214 0


B
Survival probability (%)
100
80
60
40
20
0
IPF-related mortality
+ Censored
Log-rank p=0·4622
0
100
200
300
400
Time (days)
Placebo + antacid therapy 291 288 279 265 0
Placebo + no antacid therapy 333 331 321 314 0

	FVC <70%			FVC ≥70%		
	Antacid therapy (N=144)	No antacid (N=164)	p value	Antacid therapy * (N=147)	No antacid (N=169)	p value
Progression-free survival†						
Overall‡	63 (44%)	75 (46%)	0·7971	51 (35%)	66 (39%)	0·4528
Mortality						
All-cause	14 (10%)	14 (9%)	0·7180	6 (4%)	8 (5%)	0·7787
IPF-related	9 (6%)	10 (6%)	0·9558	2 (1%)	7 (4%)	0·1382
FVC change						
Data available (n)	118	141	NA	134	156	NA
FVC change (observed; % predicted)	–5·3 (7·1)	–5·5 (7·2)	0·7899	–4·6 (5·8)	–5·4 (7·1)	0·2645
FVC change (imputed; % predicted)	–10·54 (17·24)	–10·26 (16·96)	0·8865	–7·98 (16·09)	–8·63 (16·12)	0·7239
FVC change (observed; L)	–0·22 (0·28)	–0·22 (0·29)	0·90	–0·17 (0·23)	–0·20 (0·27)	0·2757
Other outcomes						
All-cause hospital admission	39 (27%)	32 (20%)	0·1155	26 (18%)	22 (13%)	0·2487
Side-effects						
Gastrointestinal side-effects	83 (58%)	97 (59%)	0·7888	83 (56%)	77 (46%)	0·0532
Infections	107 (74%)	101 (62%)	0·0174	94 (64%)	116 (69%)	0·3781
Pulmonary infections	20 (14%)	10 (6%)	0·0214	7 (5%)	10 (6%)	0·6498

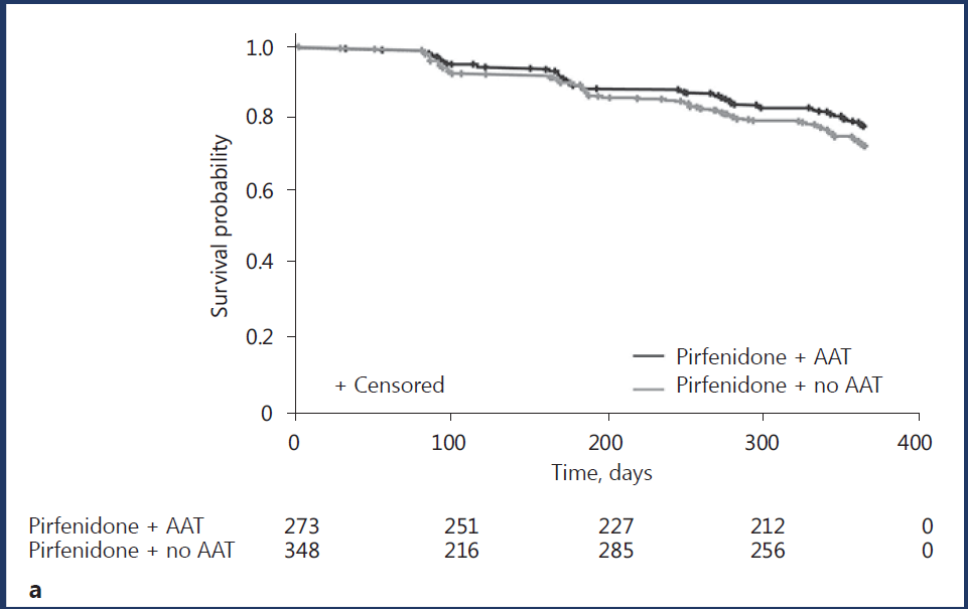
Antacid Therapy and Disease Progression in Patients with IPF Who Received Pirfenidone

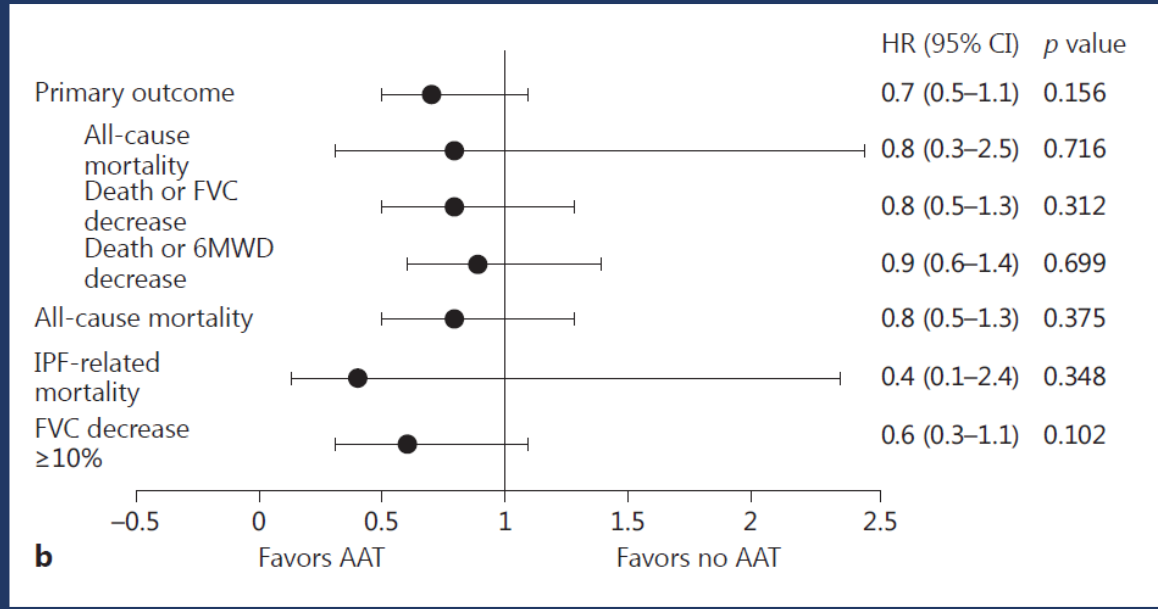
- Patients with IPF who received pirfenidone in 3 trials **(CAPACITY 004, CAPACITY 006, and ASCEND)**

- Pulmonary function, exercise tolerance, survival, hospitalizations, and adverse events (AEs) over 52 weeks were analyzed

Respiration 2017;93:415–423

Adjusted 1-year risk of progression free survival (a) and study outcomes (b)





Severe gastrointestinal AEs and severe pulmonary infections were more frequent with AAT

	FVC <70%			FVC ≥70%		
	AAT (n = 126)	no AAT (n = 165)	p value	AAT (n = 147)	no AAT (n = 169)	p value
Side effects						
GI side effects[e]	5 (4.0%)	1 (0.6%)	0.0455	5 (3.4%)	2 (1.1%)	0.1438
Infections	90 (71.4%)	122 (73.9%)	0.6332	94 (63.9%)	115 (62.2%)	0.7382
Severe pulmonary infections[e]	8 (6.3%)	3 (1.8%)	0.0446	2 (1.4%)	1 (0.5%)	0.4329
Duration of follow-up, days (mean ± SD)	338.3 ± 77.0	341.4 ± 68.2	0.7198	360.3 ± 26.3	357.2 ± 33.3	0.3387

Messages from the pooled analysis

- Antacid therapy did not yield clinically significant improvements in outcomes

- Antacid therapy did not yield synergistic or additive effect in IPF-patients on antifibrotic treatment

- Patients with advanced IPF (<70% FVC) who received antacid therapy had higher infection rates (both pulmonary and non-pulmonary)

Anti-acid therapy in IPF
: insights from the INPULSIS® trials

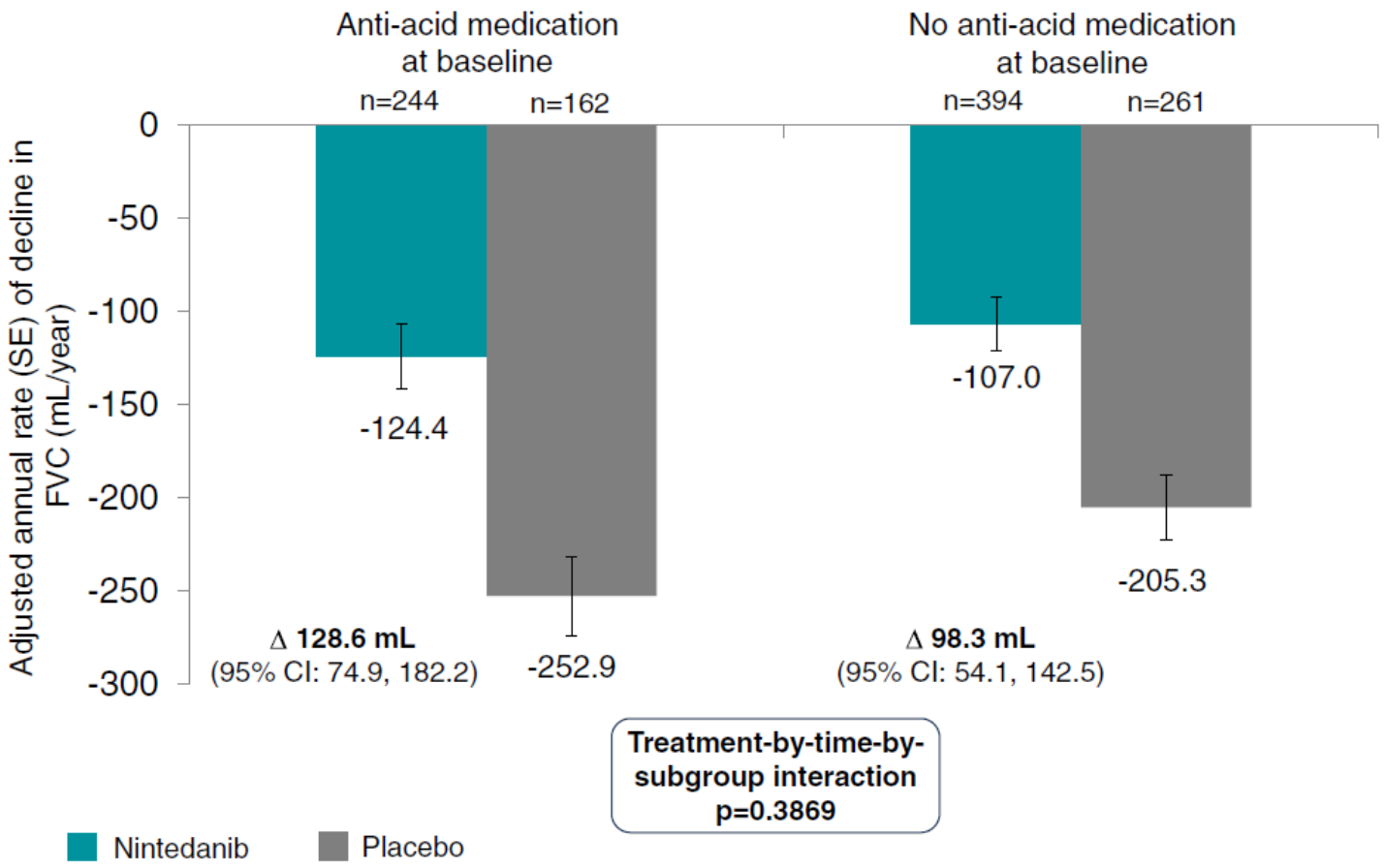
- Patients with IPF from the two INPULSIS® trials of Nintedanib

- to investigate whether anti-acid medication at baseline was associated with differences in the natural course of disease or influenced the treatment effect of nintedanib in patients with IPF

- 406 patients were receiving anti-acid medication (244 nintedanib; 162 placebo) and 655 were not (394 nintedanib; 261 placebo)

Respiratory Research (2018) 19:167

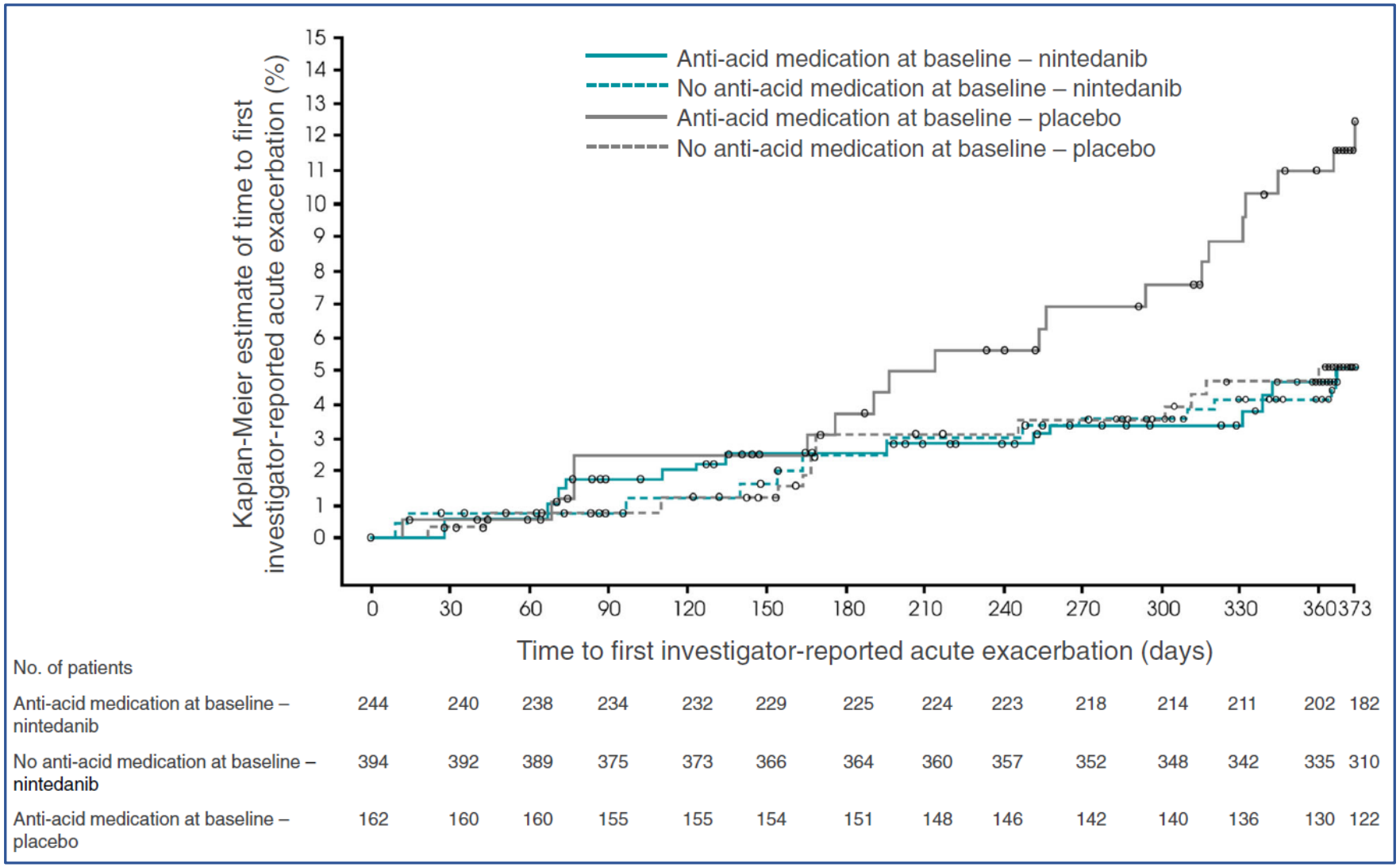
Annual rate of decline in FVC



Disease progression

N (%)	Anti-acid medication at baseline		No anti-acid medication at baseline	
	Nintedanib (n = 244)	Placebo (n = 162)	Nintedanib (n = 394)	Placebo (n = 261)
Absolute decline in FVC ≥10% predicted or death	77 (31.6)	77 (47.5)	96 (24.4)	98 (37.5)
Criterion reached first				
Absolute decline in FVC ≥10% predicted	67 (27.5)	65 (40.1)	81 (20.6)	88 (33.7)
Death	10 (4.1)	12 (7.4)	15 (3.8)	10 (3.8)
Absolute decline in FVC ≥5% predicted or death	135 (55.3)	122 (75.3)	195 (49.5)	181 (69.3)
Criterion reached first				
Absolute decline in FVC ≥5% predicted	129 (52.9)	117 (72.2)	188 (47.7)	175 (67.0)
Death	6 (2.5)	5 (3.1)	7 (1.8)	6 (2.3)

Time to first investigator-reported acute exacerbation



No. of patients														
Anti-acid medication at baseline – nintedanib	244	240	238	234	232	229	225	224	223	218	214	211	202	182
No anti-acid medication at baseline – nintedanib	394	392	389	375	373	366	364	360	357	352	348	342	335	310
Anti-acid medication at baseline – placebo	162	160	160	155	155	154	151	148	146	142	140	136	130	122

Interesting findings

- AE occurred in a greater proportion of placebo-treated patients who were receiving anti-acid medication than in those who were not (11.7% [19 patients] versus 5.0% [13 patients])

- Pneumonia was reported in a numerically higher proportion of placebo-treated patients receiving anti-acid medication than placebo-treated patients who were not

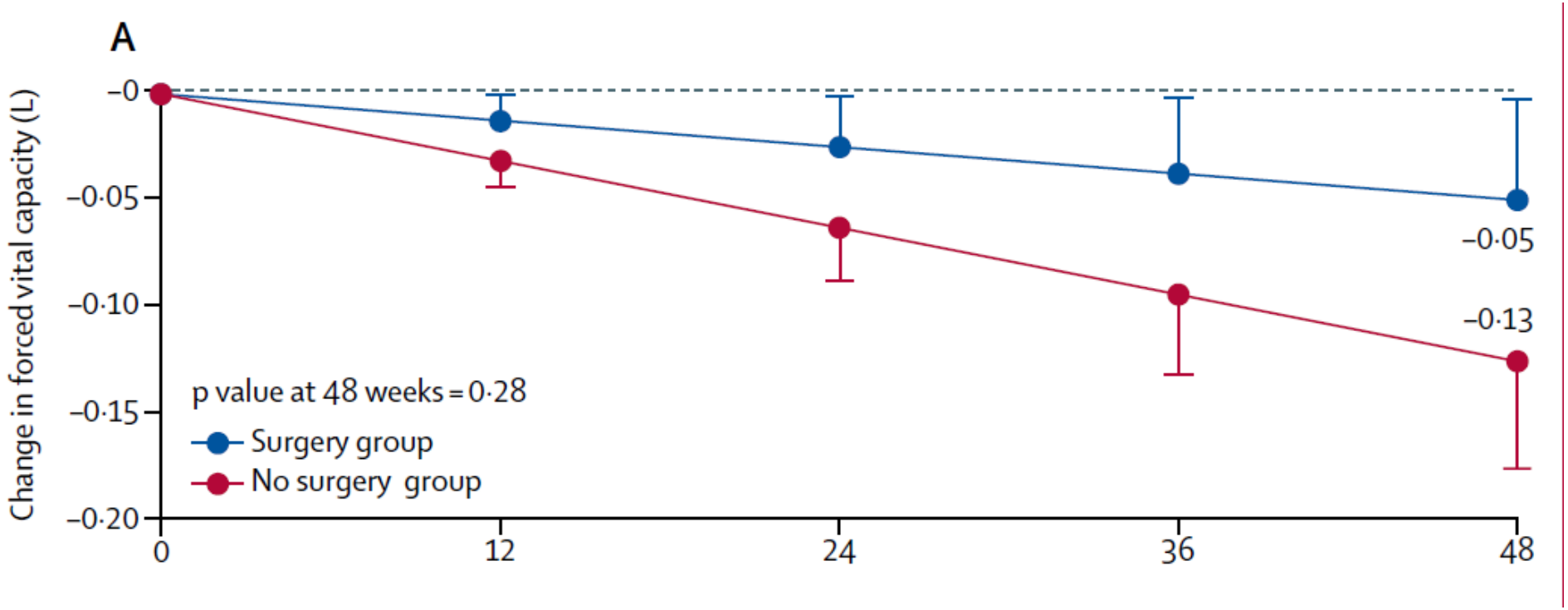
- The frequency of permanent treatment discontinuations due to diarrhea, although low, was numerically higher in patients receiving anti-acid medication

Laparoscopic anti-reflux surgery for the treatment of IPF (WRAP-IPF)

- A multicentre, randomised, controlled phase 2 trial
- Patients with IPF and abnormal acid GER (DeMeester score of ≥14·7; measured by 24-h pH monitoring)
- Concomitant therapy with nintedanib and pirfenidone was allowed
- The primary endpoint - change in FVC at week 48

Lancet Respir Med 2018; 6: 707–14

The mean change in FVC from randomization to week 48

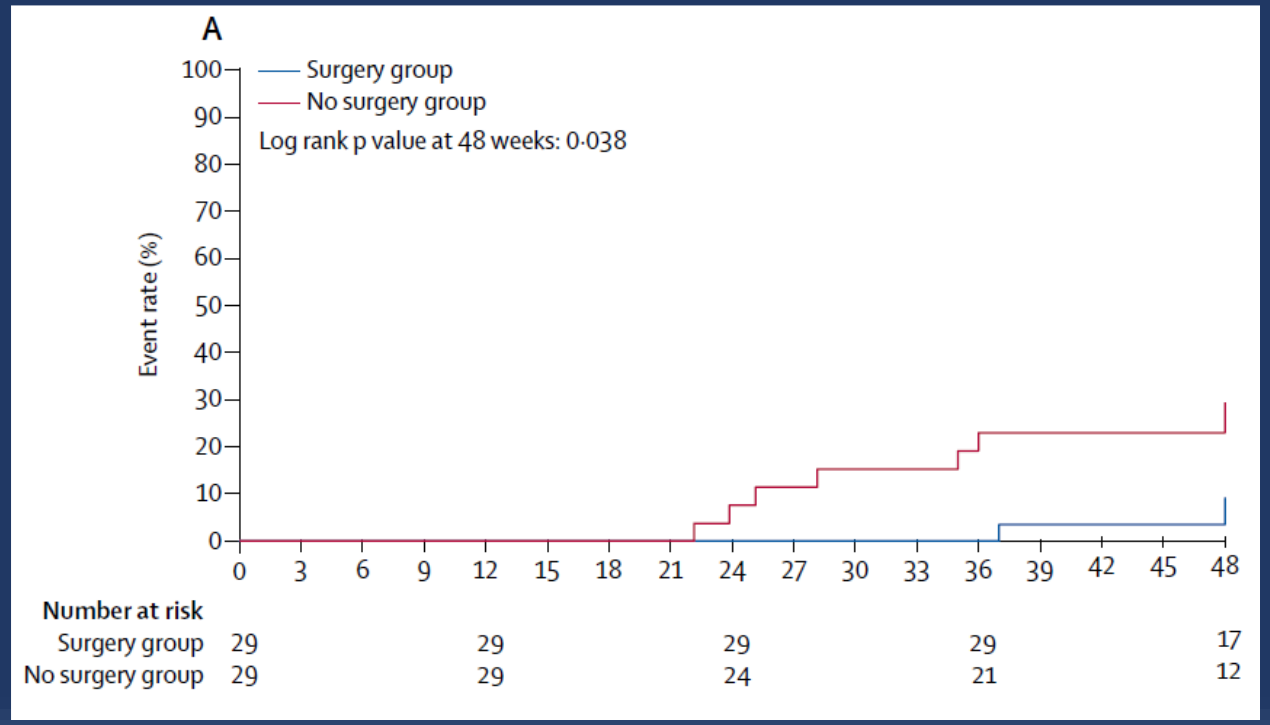


58 patients to receive surgery (n=29) or no surgery (n=29)

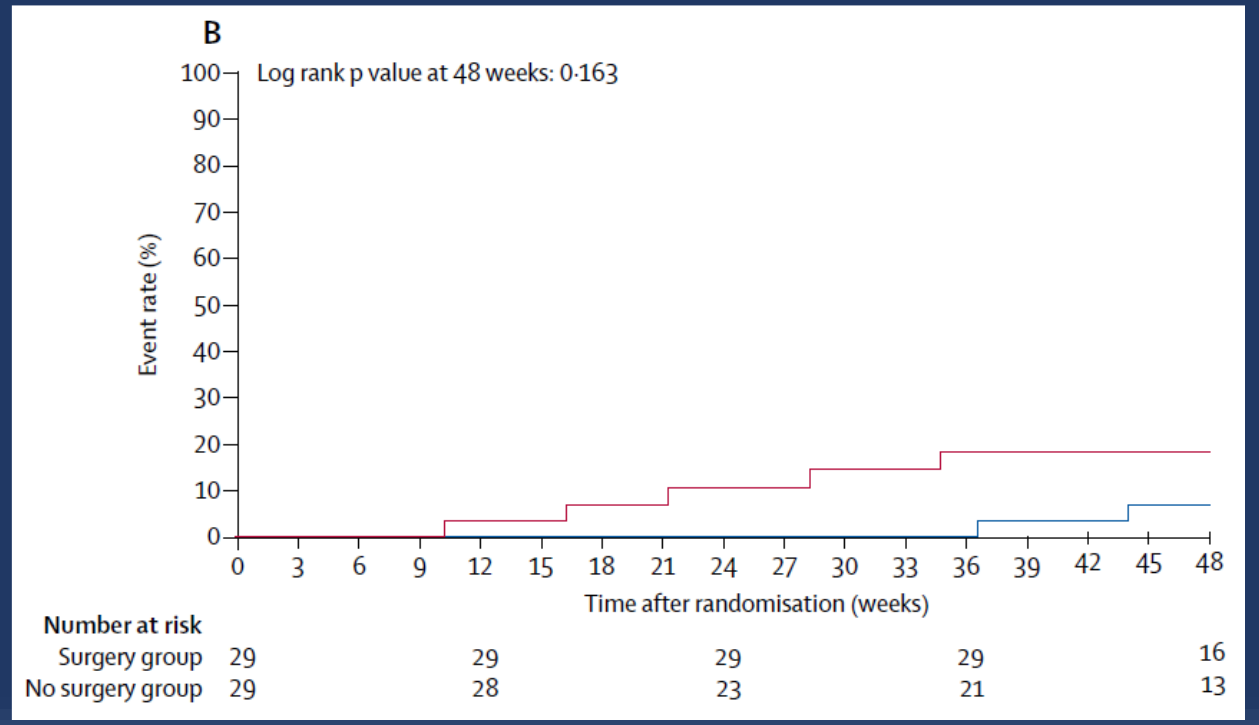
Secondary endpoints

	Surgery (n=29)	No surgery (n=29)	p value
Clinical events*			
Acute exacerbation	1 (3%)	4 (16%)	0·19
Respiratory hospitalisation	2 (7%)	6 (21%)	0·25
Non-elective hospitalisation	5 (17%)	8 (28%)	0·35
Lung transplantation	0	1 (3%)	>0·99
Disease progression†			
Death	1 (3%)	4 (18%)	0·13
10% FVC decline or death	2 (9%)	7 (29%)	0·038
10% FVC decline, acute exacerbation, or death	2 (9%)	7 (28%)	0·048
Respiratory hospitalisation or death	2 (9%)	5 (19%)	0·16
Non-elective hospitalisation or death	5 (17%)	7 (26%)	0·50
10% FVC decline, 5 point UCSD Shortness of Breath Questionnaire increase, respiratory hospitalisation, or death	15 (57%)	15 (56%)	0·74

Time to the composite endpoint of 10% decline in FVC or death



Time to the composite endpoint of respiratory hospitalisation or death



Findings

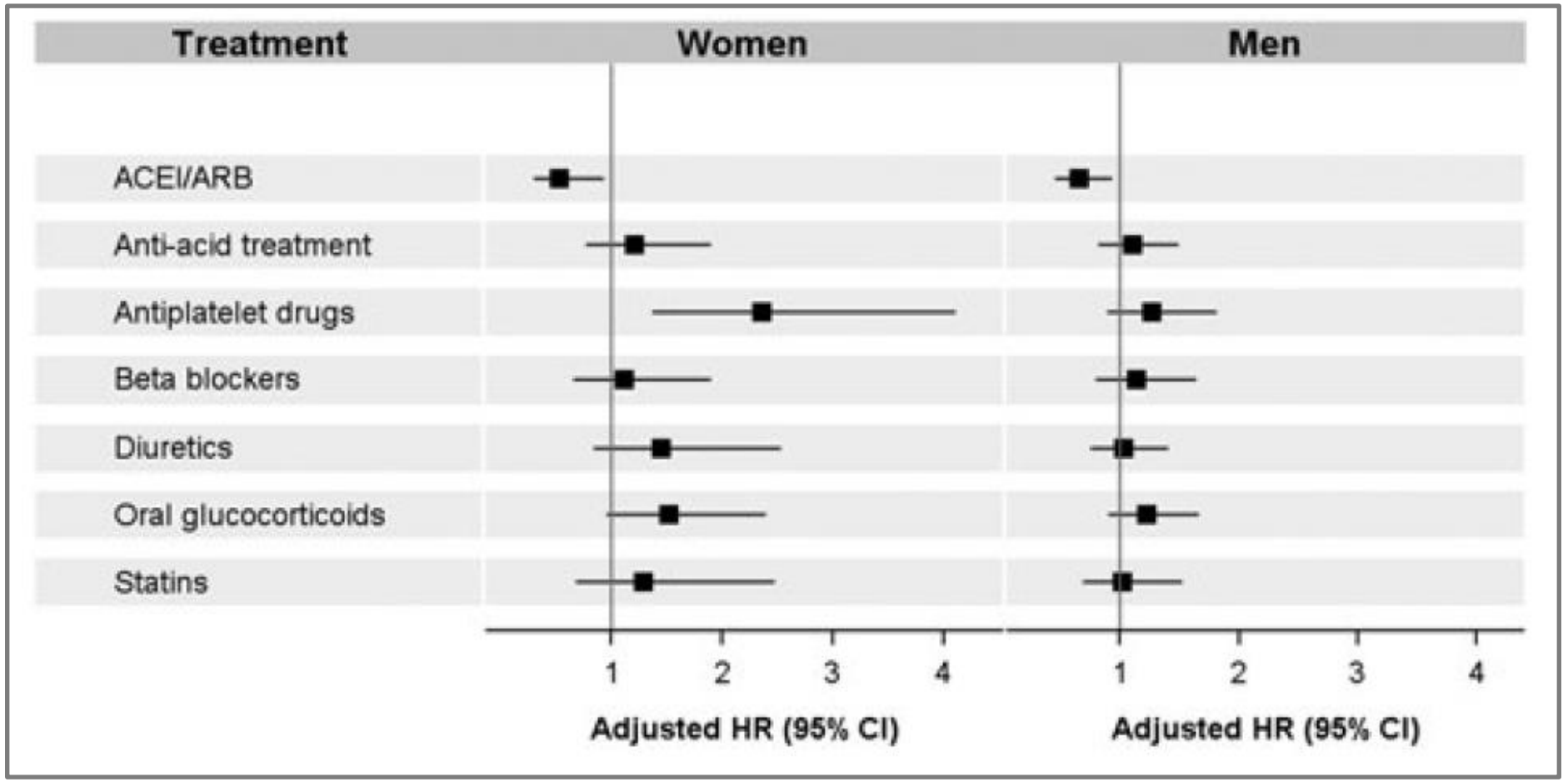
- Disease progression (change in FVC) did not reduce significantly
- Respiratory-related hospitalization and death were less common in the surgical group without statistical significance
- Some potential benefits in parameters of disease progression

Cardiovascular and antacid treatment and mortality in oxygen-dependent pulmonary fibrosis: A population-based longitudinal study

- Prospective population-based study of adults starting long-term oxygen therapy (LTOT) for pulmonary fibrosis
- 462 patients, **No patient was lost to follow-up**
- Time-dependent associations between medications and all-cause mortality were analyzed

Respirology (2016) 21, 705–711

Time-dependent effects of antacid treatment on all-cause mortality



Gastroesophageal reflux and antacid therapy in IPF : analysis from the Australia IPF Registry

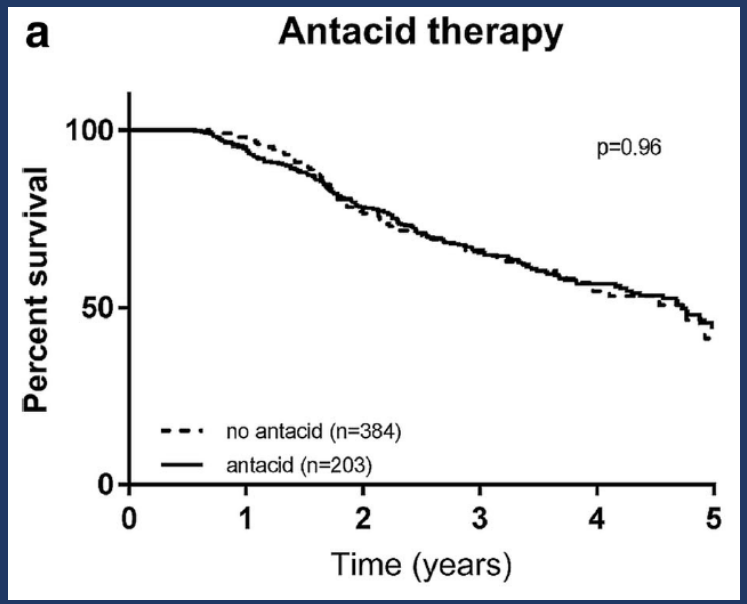
- Australian IPF Registry (N=587)
- Using prospectively collected data
- Antacid therapy (n = 384; 65%) at the time of entry into the Registry

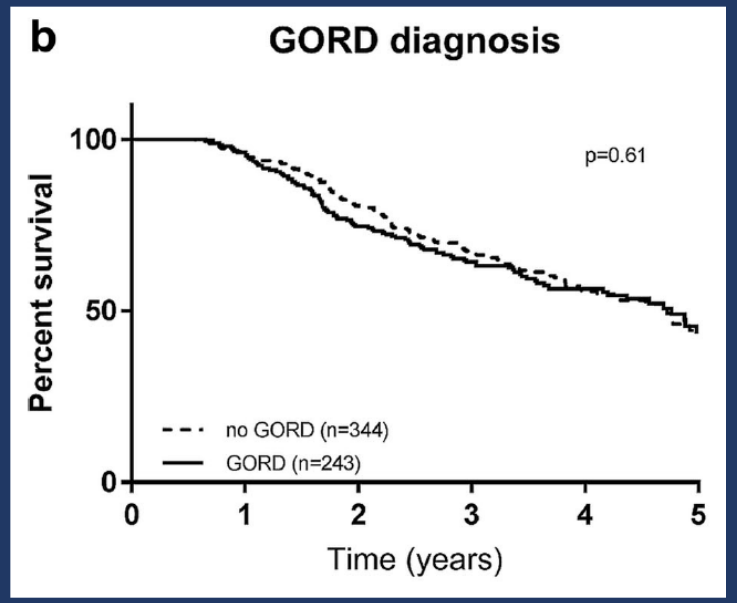
BMC Pulmonary Medicine (2019) 19:84

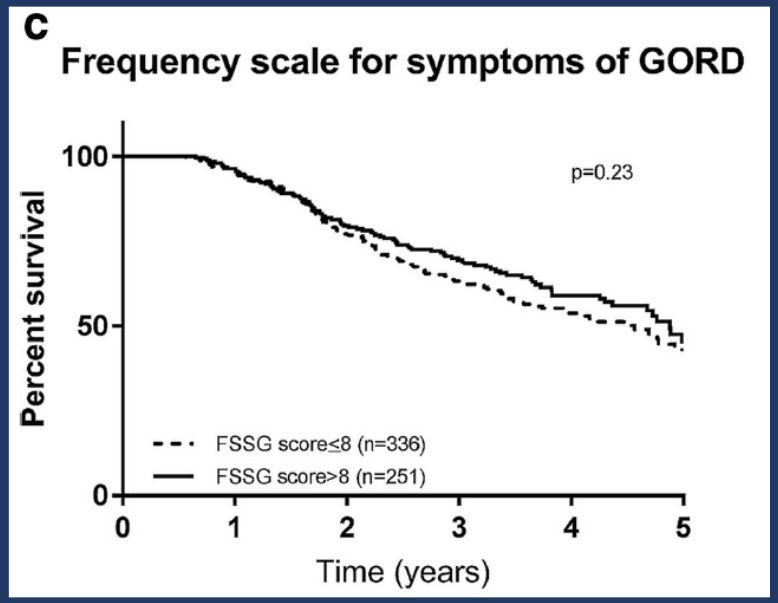
Annual decline in FVC% predicted by GORD variable

GORD variable	Yes (95% CI)	No (95% CI)	P
Antacid therapy	4.0% (3.3, 4.8%)	3.7% (2.7, 4.7%)	0.614
GORD diagnosis	4.6% (3.5, 5.4%)	3.5% (2.7, 4.4%)	0.162
Typical reflux symptoms	4.0% (3.0, 5.1%)	3.7% (3.0, 4.4%)	0.612
FSSG> 8	4.5% (3.5, 5.4%)	3.5% (2.7, 4.4%)	0.153

Kaplan Meier analysis for overall survival







No difference in survival or disease progression, regardless of antacid treatment, GORD diagnosis or GORD symptoms

Meta-analysis of Gastroesophageal Reflux Disease and Idiopathic Pulmonary Fibrosis

- To examine the evidence regarding the association between GERD and IPF

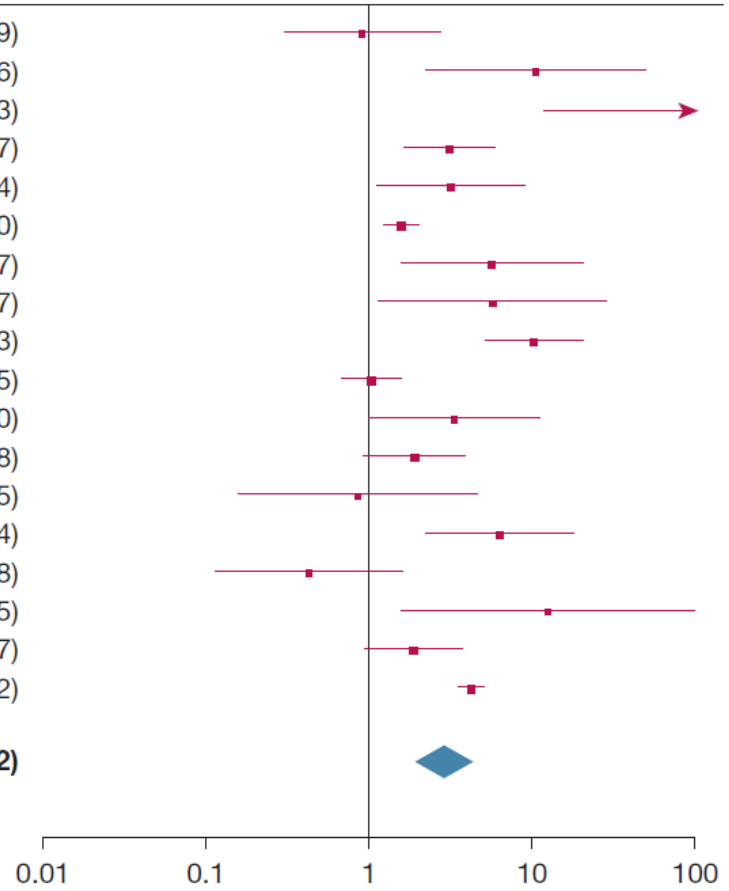
- 18 case-control studies including 3,206 patients with IPF and 9,368 control subjects

CHEST 2019; 155(1):33-43

Primary meta-analysis: association between GERD and IPF

Study or Subgroup	IPF+ GERD+	IPF+ Total	IPF– GERD+	IPF– Total	Weight	Odds Ratio M-H, Random, 95% CI
D'Ovidio 2005	8	25	12	35	5.4%	0.90 (0.30-2.69)
Embarak 2015	17	20	7	20	3.9%	10.52 (2.27-48.76)
Fahim 2011	27	40	0	50	1.7%	205.74 (11.78-3,594.83)
Garcia-Sancho 2011	23	100	23	263	7.2%	3.12 (1.66-5.87)
Gavini 2015	21	54	6	36	5.6%	3.18 (1.13-8.94)
Gribbin 2008	108	920	279	3,593	8.5%	1.58 (1.25-2.00)
Liang 2010	16	24	6	23	4.8%	5.67 (1.61-19.97)
Lo 2015	12	15	7	17	3.8%	5.71 (1.16-28.07)
Mays 1976	26	48	32	308	7.0%	10.19 (5.19-20.03)
Oldham 2015	87	196	85	196	8.1%	1.04 (0.70-1.55)
Qi 2015	16	25	8	23	5.0%	3.33 (1.02-10.90)
Raghu 2006	52	65	90	133	6.9%	1.91 (0.94-3.88)
Salvioli 2006	12	18	7	10	3.6%	0.86 (0.16-4.55)
Savarino 2013	33	40	17	40	5.6%	6.38 (2.28-17.84)
Soares 2011	9	16	21	28	4.6%	0.43 (0.12-1.58)
Tobin 1998	15	17	3	8	2.7%	12.50 (1.60-97.65)
Tossier 2016	36	78	22	70	7.1%	1.87 (0.95-3.67)
Wu 2013	333	1,505	284	4,515	8.6%	4.23 (3.57-5.02)
Total (95% CI)		**3,206**		**9,368**	**100.0%**	**2.94 (1.95-4.42)**
Total GERD+	851		909			

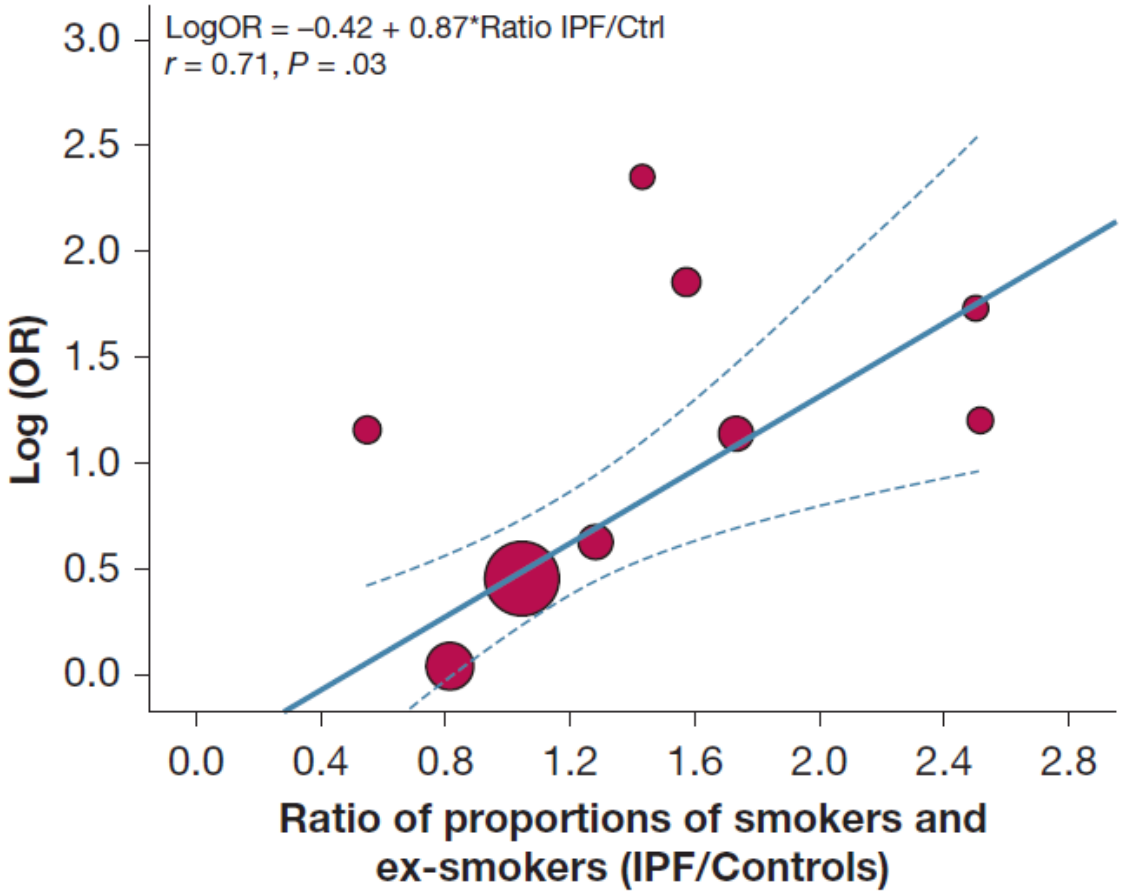
Heterogeneity: $Chi^2 = 117.57$, df = 17 ($P < .00001$); $I^2 = 86\%$



The meta-analysis indicated that GERD is associated with IPF

(OR, 2.94 [95% CI, 1.95-4.42]; P homogeneity < .0001)

In a meta regression, after controlling for smoking, GERD and IPF were not related



Treatment of Gastroesophageal Reflux in Patients With IPF

A Systematic Review and Meta-Analysis

- 8/13 observational studies were included in the meta-analysis

Study/Year	Methods	Dates	Intervention	Therapy (No.)	Control Subjects (No.)	Outcome	Newcastle-Ottawa Scale Rating
Ghebremariam et al[19]/2015	Retrospective, observational	…	PPI	130	85	Transplant-free survival	7
Kilduff et al[20]/2014	Prospective, observational	…	PPI and H2A	18	…	24-h cough count	5
Kreuter et al[13]/2016	Retrospective, observational	2011-2014	PPI and/or H2A	291	333	IPF-related mortality, all-cause mortality	8
Kreuter et al[16]/2016	Retrospective, observational	2004-2012	PPI	76	193	All-cause mortality	8
Kreuter et al[14]/2017	Retrospective, observational	2011-2014	PPI and/or H2A	273	350	IPF-related mortality, all-cause mortality	8
Lee et al[15]/2016	Retrospective, observational	2003-2015	PPI	…	…	IPF-related mortality	8
Lee et al[18]/2011	Retrospective, observational	2001-2008	PPI and/or H2A, fundoplication	96	107	Transplant-free survival	8
Lee et al[12]/2013	Retrospective, observational	2007-2011	PPI and/or H2A	124	118	All-cause mortality	7
Linden et al[7]/2006	Retrospective, observational	2001-2005	Fundoplication	14	31	Grouped pulmonary function tests, 6MWD, oxygen requirements	6
Liu et al[17]/2017	Retrospective, observational	2001-2008	PPI or H2A	34	35	All-cause mortality	7
Noth et al[21]/2012	Retrospective, observational	2005-2008	PPI and/or H2A	35	39	Grouped baseline pulmonary function tests	4
Raghu et al[22]/2006	Retrospective, observational	…	PPI	4	…	Pulmonary function tests, 6MWD	6
Raghu et al[23]/2016	Retrospective, observational	1998-2012	Fundoplication	27	…	Change in FVC % predicted	6

6MWD = 6-min walk distance; H2A = H2 receptor antagonist; IPF = idiopathic pulmonary fibrosis; PPI = proton pump inhibitor.

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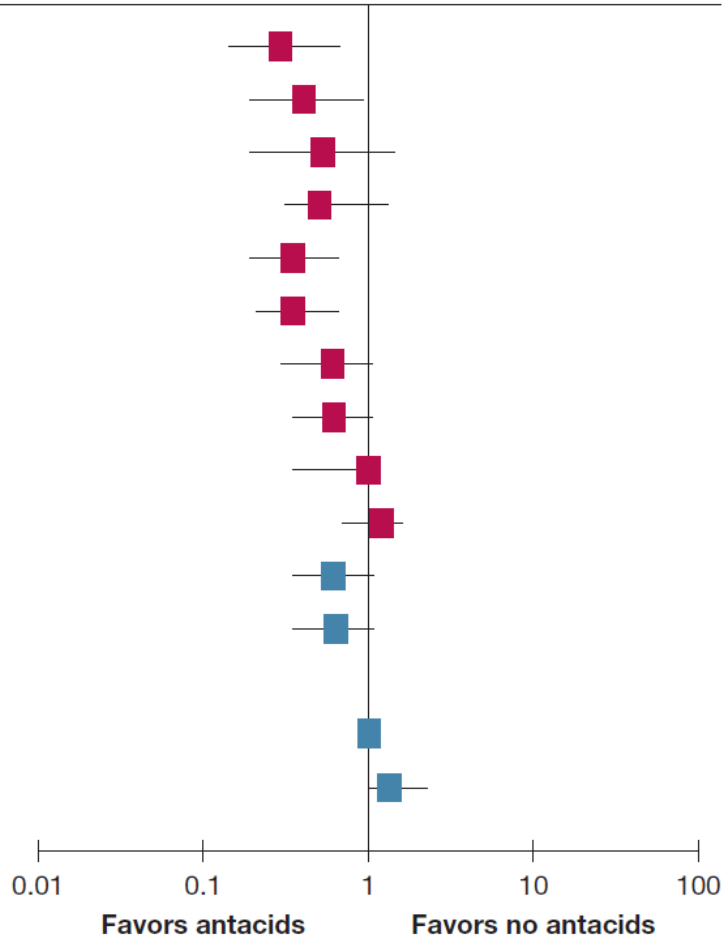
Forest plot of the effect of pharmacologic GER treatment on health outcomes

Health Outcomes	#Studies/ #Participants	Hazard Ratio/Relative Risk
IPF-related mortality (adjusted)	3/2033	0.45 (0.24-0.84)
IPF-related mortality (unadjusted)	3/2033	0.60 (0.38-0.97)
All-cause mortality (adjusted)	4/1585	0.76 (0.31-1.84)
All-cause mortality (unadjusted)	3/1316	0.73 (0.45-1.20)
Transplant-free survival (adjusted)	2/419	0.55 (0.39-0.77)
Transplant-free survival (unadjusted)	2/419	0.55 (0.41-0.74)
Progression free survival (adjusted)	2/1247	0.81 (0.61-1.08)
Progression free survival (unadjusted)	2/1247	0.86 (0.71-1.03)
Hospitalizations (adjusted)	2/1247	0.99 (0.7-1.40)
Hospitalizations (unadjusted)	2/1247	1.27 (0.86-1.88)
FVC decline >10%	2/1247	0.80 (0.59-1.08)
Decline in 6MWD >50m	2/1247	0.86 (0.70-1.06)
Adverse Events		
Infection	2/1247	1.03 (0.95-1.11)
Pulmonary infection	2/1247	1.86 (1.00-3.46)



Findings

- A significant reduction in IPF-related mortality and improved transplant-free survival (*Low-quality evidence)
- Not associated with a reduction in all-cause mortality

- Not associated with Other outcomes (FVC decline, 6MWD decline, hospitalizations, progression-free survival, St. George's Respiratory Questionnaire)
- In patients with IPF and FVC < 70%, associated with a significant increase in pulmonary infections

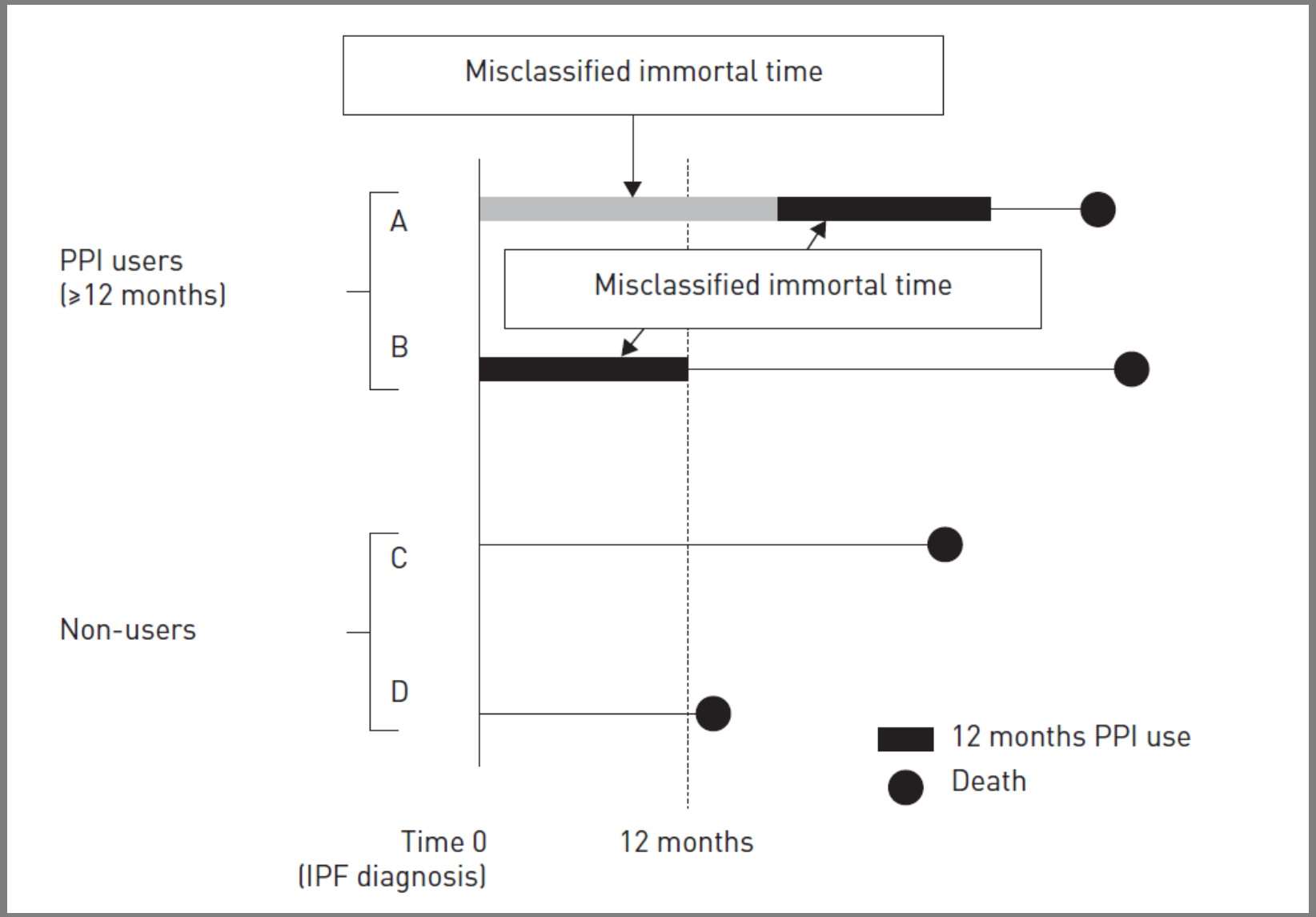
The effect of anti-acid therapy on survival in IPF : a methodological review of observational studies

- Discrepant findings on the effectiveness of anti-acid therapy on mortality in IPF

- reviewed all studies to evaluate whether immortal time bias explains these discrepancies

Eur Respir J 2018; 51: 1800376

Illustration of immortal time bias



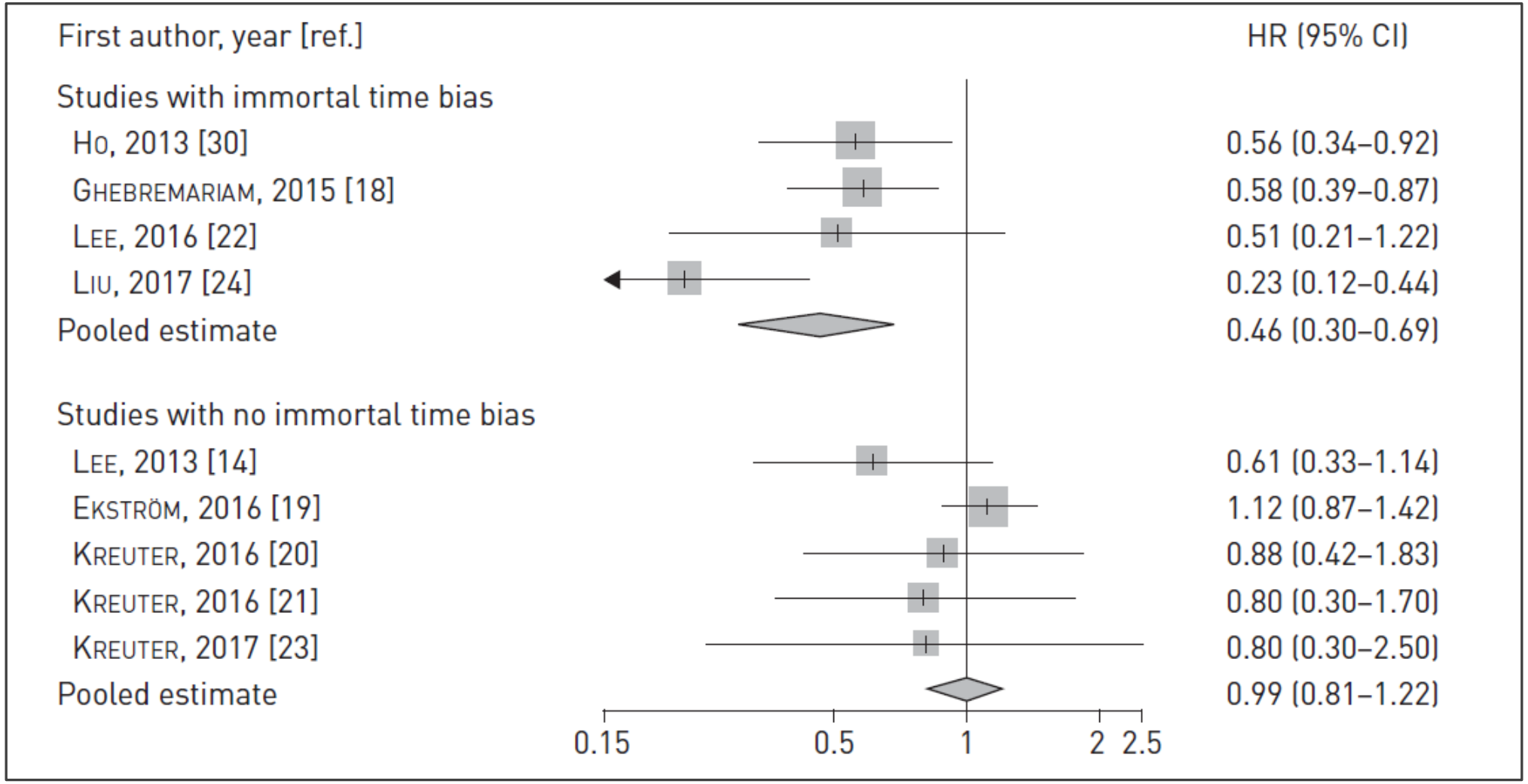
Immortal time bias in cohort studies (5)

First author, year [reference]	Sample size n	Data source	Exposure[#]	Adjusted hazard ratio (95% CI)	Duration of follow-up
Lee, 2011 [13][¶]	204	Two centres	Anti-acid therapy *versus* non-use at diagnosis	0.47 (0.24–0.93)	6 years
Ho, 2013 [30]	132	Single centre	PPIs ⩾12 months *versus* non-use	0.56 (0.34–0.92)[§]	5 years
Ghebremariam, 2015 [18]	215	Two centres	PPIs ⩾12 months *versus* non-use	0.58 (0.39–0.87)	5 years
Lee, 2016 [22][+]	786	Single centre	PPIs ⩾4 months *versus* <4 months	0.51 (0.21–1.22)	5 years
Liu, 2017 [24]	69	Single centre	Anti-acid therapy ⩾6 months *versus* <6 months	0.23 (0.12–0.44)	5 years

Observational studies, avoiding immortal time bias (5)

First author, year [reference]	Sample size n	Data source	Exposure[#]	Adjusted hazard ratio (95% CI)	Duration of follow-up
Lee, 2013 [14]	242	RCTs, placebo arms	Time-fixed at enrolment: anti-acid therapy *versus* non-use	0.61 (0.33–1.14)[¶]	30 weeks
Ekström, 2016 [19]	462	Cohort study: population-based, oxygen-dependent IPF	Time-dependent: anti-acid therapy *versus* non-use	1.12 (0.87–1.42)	4 years
Kreuter, 2016 [20]	272	Cohort study: single centre	Time-fixed at baseline: PPI use *versus* non-use	0.88 (0.42–1.83)[¶]	8 years
Kreuter, 2016 [21]	624	RCTs, placebo arms	Time-fixed at enrolment: anti-acid therapy *versus* non-use	0.80 (0.30–1.70)	1 year
Kreuter, 2017 [23]	623	RCTs, treatment arms	Time-fixed at enrolment: anti-acid therapy *versus* non-use	0.80 (0.30–2.50)	1 year

Forest plot of the association between the use of anti-acid therapy and all-cause mortality



Background of Cons

- The causal relationship between GERD and IPF – not clear
- No RCT on anti-acid treatment in IPF
- Some post hoc analyses of clinical trials do not support the benefit of antacid therapy
- No evidence additional effect in case of antifibrotic treatment
- Reports of increased gastrointestinal adverse effects and pulmonary infections –risk and benefit

My conclusion

- **Conditional recommendations for use anti-acid therapy**

  - No strong evidences at present and not equal to the evidences for antifibrotics

- **Patients who are already treated with antifibrotics**

  - The effect of anti-acid therapy may be too small to be meaningful

- **Anti-reflux surgery**

  - Very early step, need more data in the future studies

첨언

- 기존의 RCT post hoc analysis 에서 포함된 환자는 severe group이 포함되어 있지않다 (예. patients awaiting lung transplantation or severely decreased lung function)

- Sweden 연구 코호트 환자는 LTOT (산소투여)를 하고 있는 severe group이 주 환자군이었다.

- 이 두 그룹 환자 (severe vs non-severe) 모두에서 anti-acid therapy 는 별 도움이 되지못하였다.