Antacid therapy and disease outcomes in idiopathic pulmonary fibrosis: a pooled analysis

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Summary

Background Gastro-oesophageal reflux disease is a potential risk factor for the development and progression of idiopathic pulmonary fibrosis (IPF). We aimed to investigate the effect of antacid therapy on disease progression in patients randomly assigned to placebo through analysis of three large, phase 3 trials of pirfenidone in IPF.

Methods Patients with IPF from the placebo groups of three trials of pirfenidone (CAPACITY 004, CAPACITY 006, and ASCEND) were included in this post-hoc analysis. We analysed effects of antacid therapy use from baseline for pulmonary function, exercise tolerance, survival, hospital admission, and adverse events for 52 weeks with and without adjustment for potential confounders. The primary endpoint, disease progression by 1 year, was defined as a decrease in predicted forced vital capacity (FVC) by 10% or more, a decrease in 6 min walk distance (6MWD) by 50 m or more, or death. We did survival analyses with the Kaplan-Meier estimator and evaluated using the log-rank test.

Findings Of 624 patients, 291 (47%) received antacid therapy and 333 (53%) did not. At 52 weeks, we noted no significant difference between groups for disease progression (114 [39%] for antacid therapy *vs* 141 [42%] for no antacid therapy, p=0·4844). Rates also did not differ for all-cause mortality (20 [7%] *vs* 22 [7%], p=0·8947), IPF-related mortality (11 [4%] *vs* 17 [5%]; p=0·4251), absolute FVC decrease by 10% or more (49 [17%] *vs* 64 [19%]; p=0·4411), or mean observed change in FVC (% predicted –4·9% [SD 6·4] *vs* –5·5% [7·2], p=0·3355; observed volume –0·2 L [0·3] *vs* –0·2 L [0·3], p=0·4238). The rate of hospital admission was non-significantly higher in the antacid therapy group (65 [22%] *vs* 54 [16%]; p=0·0522). When stratified by baseline FVC (<70% or ≥70%), disease progression, mortality, FVC, 6MWD, and hospital admission did not differ between groups. Adverse events were similar between treatment and no treatment groups; however, overall infections (107 [74%] *vs* 101 [62%]; p=0·0174) and pulmonary infections (20 [14%] *vs* 10 [6%]; p=0·0214) were higher in patients with advanced IPF (ie, FVC <70%) who were treated with antacids than not treated with antacids.

Interpretation Antacid therapy did not improve outcomes in patients with IPF and might potentially be associated with an increased risk of infection in those with advanced disease.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, irreversible, and progressive lung disease of unknown cause with a median survival from the time of diagnosis of 2–3 years.[1] It is characterised by a progressive decrease in lung function, worsening dyspnoea, and diminished exercise tolerance. Two drugs, pirfenidone and nintedanib, are approved for the treatment of the disorder; both have shown significant slowing of disease progression compared with placebo.[2–4]

Gastro-oesophageal reflux disease is prevalent in 10–20% of people living in high-income countries and its symptoms include heartburn, dyspepsia, regurgitation, and chest pain.[5] Diagnosis can be established by a combination of symptoms, endoscopy testing, ambulatory reflux monitoring, and response to antacid therapy. Recommended treatments include lifestyle interventions—such as weight loss, head-of-bed elevation, tobacco and alcohol cessation, avoidance of late-night meals, and cessation of foods that can potentially aggravate reflux symptoms—and the use of antacids with histamine H2-receptor antagonists (H2 blockers) or proton-pump inhibitors.[5]

The incidence of gastro-oesophageal reflux disease in patients with IPF is higher than that in the general population, and it has been reported to range between 8% and 87%;[6–9] variations in incidence might depend on the method of diagnosis used—such as patient-reported symptoms, physician reports, or pH probe testing—and the variability between sites in the collection and reporting of information. The increased incidence of the disease in patients with IPF could be due to shared risk factors for these disorders, including age and smoking.[10] Additionally, the increased recoil of the fibrotic lung could dilate the lower oesophageal sphincter and potentially increase reflux. Gastro-oesophageal reflux disease might also have an important role in the development and progression of IPF, including acute exacerbations.[11,12] In fact, gastro-oesophageal reflux disease is a risk factor for

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Research in context

Evidence before this study

We searched PubMed for studies published before Jan 25, 2016, with no language restrictions, using the search terms "antacid therapy", "proton pump inhibitors", "gastroesophageal reflux", and "idiopathic pulmonary fibrosis". In the recently updated 2015 ATS/ERS/JRS/ALAT guidelines on treatment of idiopathic pulmonary fibrosis (IPF), antacid therapy has been given a conditional recommendation for use. This recommendation, which is unchanged from the 2011 guideline document, is based on observational and retrospective studies and post-hoc analysis of patients randomly assigned to placebo in clinical trials of pharmacological interventions, the results of which suggested that patients given antacid therapy had slower disease progression as assessed by decrease in forced vital capacity and improved survival compared with patients not receiving antacid therapy.

Added value of this study

By contrast with previous reports, in this study, which analysed patients randomly assigned to placebo in three large clinical trials of pirfenidone, antacid therapy was not associated with a slower disease progression in IPF. Additionally, in patients with advanced disease (eg, with a forced vital capacity of less than 70%) antacid therapy was associated with a significantly higher incidence of pulmonary and non-pulmonary infections.

Implications of all the available evidence

Although clinicians might reasonably offer antacid therapy to patients with IPF with symptomatic gastro-oesophageal reflux, our data do not support a previously reported benefit of antacid therapy in patients with IPF. Present guidelines give a conditional recommendation for use of antacid therapy in patients with IPF, but overall, the available evidence is inconsistent. Long-term, randomised, placebo-controlled studies are needed to investigate the effect of antacid therapy in patients with IPF, particularly those with advanced disease.

microaspiration, which might cause repeated lung injury and worsening of IPF. Antacid therapy might decrease the risk for acidic microaspiration-associated lung injury or damage.[13–15]

Present guidelines for treatment of IPF give a conditional recommendation for the use of antacid therapy in patients with the disorder, albeit with very low confidence in estimates of effect[16] because data on antacid therapy's effect on outcomes in the disorder are limited. However, a retrospective analysis[11] of patients with IPF reported that gastro-oesophageal reflux disease-related treatment, especially antacid therapy, was associated with less radiological fibrosis and was an independent predictor of increased survival time. An additional study[17] reported on the outcome of patients with IPF randomly assigned to placebo in three National Heart, Lung, and Blood Institute IPF Clinical Research Network (IPFnet)-sponsored randomised controlled trials. After adjusting for sex and pulmonary function, patients who received antacid therapy had significantly less deterioration of pulmonary function than those not being treated.

The objective of this study was to further investigate the effect of antacid therapy on the composite endpoint of disease progression in patients randomly assigned to placebo in three large, phase 3 trials of pirfenidone in IPF.

Methods

Source and study populations

The study population included all individuals with IPF randomly assigned to placebo in three phase 3 multinational trials (CAPACITY studies 004 and 006 and the ASCEND 016 study), which were active between 2011 and 2014.[2,3] Eligibility criteria for the trials have been previously described.[2,3] Briefly, inclusion criteria included age 40–80 years; a diagnosis of IPF made within the previous 48 months; no evidence of improvement in disease severity in the previous year; a predicted forced vital capacity (FVC) of 50% or more; haemoglobin-corrected predicted diffusing capacity of the lung for carbon monoxide (DLCO) of 35% or more (≥30% in ASCEND); either a predicted FVC or a predicted DLCO of 90% or less (both ≤90% in ASCEND); and a 6 min walk distance (6MWD) of 150 m or more. All trial participants provided written informed consent, and the ethics committee or institutional review board at each participating institution approved the protocol for each trial. The study population was stratified into two subgroups on the basis of use of antacid therapy (ie, yes *vs* no; either H2 blockers or proton-pump inhibitors) at trial baseline.

Data collection

Data collected from the three trials included patient demographic and clinical characteristics (eg, age, sex, and comorbidity profile), pulmonary function (eg, FVC and DLCO), exercise tolerance (6MWD), dyspnoea (University of California at San Diego Shortness of Breath Questionnaire [UCSD-SOBQ]), drug use (eg, H2 blockers and proton-pump inhibitors) and indication for use, adverse events, admissions to hospital, and vital status. The total score of the UCSD-SOBQ ranges from 0 to 120 and increases with extent of dyspnoea.[18]

	Antacid therapy (N=291)	No antacid therapy (N=333)	p value
Age (years)			
Mean (SD)	67·3 (7·4)	67·0 (7·7)	0·5753
Median (IQR)	68 (62–73)	68 (62–73)	..
Sex			
Male	212 (73%)	253 (76%)	0·3717
Female	79 (27%)	80 (24%)	0·3717
Physiological			
FVC (% predicted)	72·8 (14·9)	71·3 (12·3)	0·1522
DLCO (% predicted)	45·8 (10·2)	45·4 (11·9)	0·6108
6MWD	407·6 (96·6)	415·5 (92·1)	0·2978
Dyspnoea			
UCSD-SOBQ	34·8 (20·8)	35·0 (22·3)	0·9300
Medical history			
Comorbidities			
Cardiovascular disease	96 (33%)	84 (25%)	0·0327
Chronic respiratory failure	10 (3%)	10 (3%)	0·7591
COPD	10 (3%)	12 (4%)	0·9101
Pulmonary embolism	4 (1%)	2 (1%)	0·3230
Pulmonary hypertension	8 (3%)	11 (3%)	0·6877
Atrial fibrillation	7 (2%)	22 (7%)	0·0129
Sleep apnoea	62 (21%)	33 (10%)	<0·0001
Gastrointestinal comorbidities			
GERD	247 (85%)	74 (22%)	<0·0001
Hiatus hernia	48 (16%)	13 (4%)	<0·0001
Barrett's oesophagus	6 (2%)	1 (<1%)	0·0371
HP-positive gastritis	1 (<1%)	0	0·2844
Cardiovascular risk factors			
Hypertension	179 (62%)	161 (48%)	0·0010
Smoker (current/former)	183 (63%)	201 (60%)	0·5176
Diabetes	57 (20%)	77 (23%)	0·2833
Hypercholesterolaemia	160 (55%)	135 (41%)	0·0003
Obesity (BMI >30 kg/m²)	123 (42%)	142 (43%)	0·9248
PPI use only	256 (88%)	NA	NA
H2 use only	24 (8%)	NA	NA
PPI plus H2 use	11 (4%)	NA	NA

Data are mean (SD) or n (%), unless stated otherwise. FVC=forced vital capacity. DLCO=haemoglobin-corrected predicted diffusing capacity of the lung for carbon monoxide. 6MWD=6 min walk distance. UCSD-SOBQ=University of California at San Diego Shortness of Breath Questionnaire. COPD=chronic obstructive pulmonary disease. GERD=gastro-oesophageal reflux disease. HP=*Helicobacter pylori*. BMI=body-mass index. PPI=proton-pump inhibitor. H2=histamine H2-receptor antagonist. NA=not applicable.

Table 1: **Baseline demographics and clinical characteristics**

	CAPACITY 004 (N=71)	CAPACITY 006 (N=79)	ASCEND 016 (N=141)	Pooled (N=291)
GERD	58 (82%)	67 (85%)	120 (85%)	245 (84%)
Dyspepsia	0	3 (4%)	5 (4%)	8 (3%)
Gastritis	3 (4%)	0	5 (4%)	8 (3%)
Ulcer	1 (1%)	1 (1%)	5 (4%)	7 (2%)
Prophylaxis	4 (6%)	1 (1%)	2 (1%)	7 (2%)
Hiatus hernia	3 (4%)	2 (3%)	1 (1%)	6 (2%)
Other	2 (3%)	2 (3%)	1 (1%)	5 (2%)
Non-specific gastrointestinal disease	0	2 (3%)	0	2 (1%)
Indigestion	0	0	1 (1%)	1 (<1%)
Barrett's oesophagus	0	0	1 (1%)	1 (<1%)
Nausea	0	1 (1%)	0	1 (<1%)

Data are n (%). PPI=proton-pump inhibitor. H2 blockers=histamine H2-receptor antagonists. GERD=gastro-oesophageal reflux disease.

Table 2: **Indications for use of antacid therapy (PPIs or H2 blockers, or both)**

	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			
Absolute decrease ≥10%	49 (17%)	64 (19%)	0·4411
Relative decrease ≥10%	91 (31%)	94 (28%)	0·4063
Absolute decrease ≥5%	126 (43%)	130 (39%)	0·2805
Relative decrease ≥5%	155 (53%)	170 (51%)	0·5808
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
Length of follow-up (days)	343 (66)	347 (62)	0·3811

Data are n (%) or mean (SD). FVC=forced vital capacity. 6MWD=6 min walk distance. IPF=idiopathic pulmonary fibrosis. *All patients considered in analyses, unless otherwise noted. †Only first event considered in analyses. ‡FVC decrease ≥10%, 6MWD decrease ≥50 m, or death. §Only confirmed cases included, defined as those for which follow-up assessment was repeated ≥6 weeks after initial assessment and criteria for outcome were met. ¶All patients were considered in this analysis.

Table 3: **Unadjusted 1 year risk of study outcomes by antacid therapy**

The trial investigators measured FVC, 6MWD, and UCSD-SOBQ at trial baseline and periodically during the trials; in the CAPACITY trials, investigators assessed DLCO after baseline only. Investigators documented drug use at trial baseline and subsequently during the trials. They assessed vital status at prespecified timepoints until the follow-up visit or entry into an extension study, whichever occurred earlier. An independent mortality assessment committee in the ASCEND trial[3] and the site investigators in the CAPACITY trials[2] assessed the primary cause of death and its relation to IPF using a blinded method. The investigators reported safety

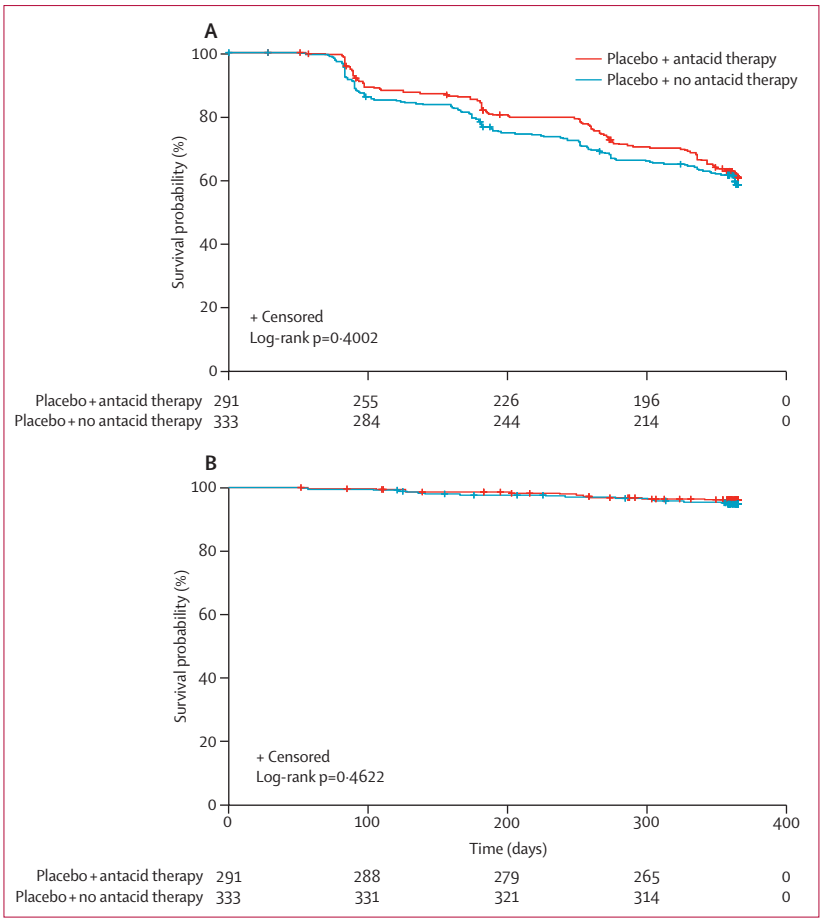

Figure: **Unadjusted 1 year risk of (A) progression-free survival and (B) IPF-related mortality**
Progression-free survival was defined as the time to the first occurrence of confirmed decrease of ≥10% predicted FVC, a confirmed decrease of ≥50 m in the 6MWD, or death. IPF=idiopathic pulmonary fibrosis. FVC=forced vital capacity. 6MWD=6 min walk distance.

outcomes as events that occurred during the time period from baseline to 28 days after the last dose of the study drug. The CAPACITY trials' duration was 72–120 weeks, and the ASCEND trial duration was 52 weeks.

See Online for appendix

Outcomes

We defined the primary study outcome, disease progression, as death due to any reason, absolute FVC decrease by 10% or more, or 6MWD decrease by 50 m or more, occurring within 1 year of trial baseline. We only regarded functional worsening (FVC decrease ≥10% or 6MWD decrease ≥50 m) as disease progression when it was reported on two consecutive occasions, at least 6 weeks apart. We defined progression-free survival as time to the first occurrence of any of the following: a confirmed 10% or more decrease in predicted FVC, a confirmed 50 m or more decrease in the 6MWD, or death. Secondary outcomes included all-cause and IPF-related mortality, absolute FVC decrease of 10% or more, relative FVC decrease of 10% or more, absolute FVC decrease of 5% or more, relative FVC decrease of 5% or more, all-cause hospital admission, and selected adverse events (gastrointestinal adverse effects, infections, and pulmonary infections).

Statistical analysis

We assessed demographic and clinical characteristics of the study population both separately by trial and collectively; we also stratified these characteristics by baseline use of antacid therapy. We compared crude (ie, unadjusted) risks of binary study outcomes, and changes from baseline in FVC and 6MWD, between baseline users of antacid therapy and baseline non-users. We did statistical comparisons using an independent-samples *t* test for continuous variables and a χ^2 test for categorical variables.

We examined antacid therapy use against study outcomes using a shared frailty model (an extension of the Cox proportional hazards model that adjusts for intracluster [ie, intra-trial] correlation), with and without adjustment for age, sex, smoking status, lung function, and comorbidity profile. Survival analyses were based on the Kaplan-Meier estimator and we evaluated them using the log-rank test. We only used observed data—ie, missing values were not imputed. We censored individuals at the time of loss to follow-up, at the time of lung transplantation, or at the end of the 1 year follow-up period, whichever occurred first. We evaluated the presence of multicollinearity, hazards assumptions, and the treatment of death as a competing risk (where appropriate) using published methods.[19,20] SAS version 9.3 was used for all statistical analyses.

Role of the funding source

This was an investigator-initiated analysis. The funder of the study oversaw the study design and data collection. All authors had access to all of the data in the study and interpreted them. The corresponding author had final responsibility for the decision to submit for publication.

Results

A total of 624 patients were included in the study cohort. Overall, baseline demographics and clinical characteristics for patients in both groups were similar (appendix). Of the 624 patients, 291 (47%) patients received antacid therapy (256 [88%] proton-pump inhibitors, 24 [8%] H2 blockers, 11 [4%] proton-pump inhibitors and H2 blockers; table 1). Of the 291 patients receiving antacid therapy, 38 (13%) stopped after baseline; of the 333 patients not receiving antacid therapy, 83 (25%) patients started after baseline. Baseline characteristics were similar between antacid therapy users and non-users, with the exception of a higher proportion of antacid therapy users having sleep apnoea, gastro-oesophageal reflux disease, hiatus hernia, or Barrett's oesophagus compared with patients who did not receive antacid therapy. Cardiovascular risk factors were also more prevalent in the antacid therapy group, with higher rates of hypertension and hypercholesterolaemia than in the

	FVC <70%			FVC ≥70%		
	Antacid therapy* (N=144)	No antacid therapy* (N=164)	p value	Antacid therapy* (N=147)	No antacid therapy* (N=169)	p value
Progression-free survival†						
Overall‡	63 (44%)	75 (46%)	0·7971	51 (35%)	66 (39%)	0·4528
All-cause mortality	8 (6%)	12 (7%)	0·5313	6 (4%)	6 (4%)	0·8053
FVC decrease (absolute) ≥10%§	13 (9%)	19 (12%)	0·4630	19 (13%)	18 (11%)	0·5305
6MWD decrease ≥50 m§	42 (29%)	44 (27%)	0·6482	26 (18%)	42 (25%)	0·1221
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						
Absolute decrease ≥10%	26 (18%)	36 (22%)	0·3949	23 (16%)	28 (17%)	0·8242
Relative decrease ≥10%	61 (42%)	55 (34%)	0·1108	30 (20%)	39 (23%)	0·5668
Absolute decrease ≥5%	68 (47%)	59 (36%)	0·0454	58 (39%)	71 (42%)	0·6447
Relative decrease ≥5%	86 (60%)	90 (55%)	0·3914	69 (47%)	80 (47%)	0·9436
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						
6MWD decrease ≥50 m¶	42 (29%)	49 (30%)	0·8914	30 (20%)	45 (27%)	0·1950
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
Length of follow-up (days)	337 (73)	342 (71)	0·5461	349 (58)	353 (51)	0·5252

Data are n (%) or mean (SD). FVC=forced vital capacity. 6MWD=6 min walk distance. IPF=idiopathic pulmonary fibrosis. NA=not applicable. *All patients considered in analyses, unless otherwise noted. †Only first event considered in analyses. ‡FVC decrease ≥10%, 6MWD decrease ≥50 m, or death. §Only confirmed cases included, defined as those for which follow-up assessment was repeated ≥6 weeks after initial assessment and criteria for outcome were met. ¶All patients were considered in this analysis.

Table 4: **Unadjusted 1 year risk of study outcomes by antacid therapy and baseline FVC**

no antacid therapy group. Antacid therapy was prescribed mainly for gastro-oesophageal reflux disease (245 [84%] patients), followed by dyspepsia (eight [3%] patients) and gastritis (eight [3%] patients; table 2).

Mean follow-up was similar between groups (343 days for antacid therapy *vs* 347 days for no antacid therapy; p=0·3811; table 3). Antacid therapy did not result in a significant between-group difference for disease progression versus no antacid therapy in the unadjusted analysis (39% *vs* 42%, p=0·4844; table 3). In the Kaplan-Meier analysis antacid therapy users had similar disease progression at 1 year compared with no antacid therapy users (37·8% *vs* 40·5%; p=0.4002; figure). For each component of the disease progression composite endpoint, a similar number of patients in the antacid therapy and no antacid therapy groups had each qualifying event (ie, death, absolute FVC decrease by 10% or more, and decrease of 50 m or more in the 6MWD; table 3). In both groups, the rates of all-cause mortality and IPF-related mortality were also similar, irrespective of antacid therapy (table 3). The risk of death from IPF at 1 year was not significantly reduced with antacid therapy compared with no antacid therapy (3·9% *vs* 5·2%; p=0·4622; figure). Antacid therapy users had similar mean observed changes in FVC from baseline to week 52 compared with no antacid therapy users (table 3). Absolute and relative changes in percentage FVC from baseline and 6MWD decreases by 50 m or more after 52 weeks were similar between patients who did and did not receive antacid therapy (table 3). We noted a non-significantly higher rate of hospital admission in the antacid therapy group compared with the no antacid therapy group (p=0·0522; table 3).

When patients were stratified by baseline FVC (≥70% or <70%; table 4), no differences were observed in disease progression or mortality between the two groups. Of 144 patients with less than 70% predicted FVC, disease progression rates were 63 (44%) for patients who received antacid therapy compared with 75 (46%) for those who did

	Progression-free survival*		All-cause mortality		Death or FVC decrease ≥10%		Death or 6MWD decrease ≥50 m		All-cause hospital admission*		IPF-related mortality	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Unadjusted												
Antacid therapy	0·9 (0·7–1·2)	0·404	1·1 (0·6–1·9)	0·853	1·0 (0·8–1·3)	0·996	0·9 (0·7–1·2)	0·407	1·5 (1–2·1)	0·043	0·8 (0·4–1·6)	0·464
Adjusted												
Antacid therapy	0·9 (0·6–1·3)	0·533	0·8 (0·3–1·7)	0·495	1·0 (0·7–1·5)	0·982	0·9 (0·6–1·2)	0·361	1·2 (0·7–1·9)	0·473	0·4 (0·2–1·1)	0·077
Age (per 5-unit change)	0·99 (0·902–1·088)	0·841	0·954 (0·764–1·192)	0·680	0·919 (0·833–1·013)	0·087	1·035 (0·941–1·138)	0·482	1·073 (0·935–1·230)	0·315	0·910 (0·685–1·210)	0·516
Sex (male *vs* female)	0·8 (0·6–1·1)	0·246	1·6 (0·7–3·7)	0·274	1·0 (0·7–1·4)	0·873	0·8 (0·6–1·1)	0·174	0·7 (0·5–1·1)	0·118	1·3 (0·5–3·5)	0·618
Smoking status (current/former *vs* never)	1·0 (0·8–1·3)	0·978	2·9 (1·2–7)	0·021	1·0 (0·7–1·3)	0·911	1·1 (0·8–1·5)	0·412	1·0 (0·7–1·6)	0·846	2·7 (1–7·2)	0·054
FVC, % predicted (per 5-unit change)	0·969 (0·915–1·026)	0·274	0·927 (0·798–1·077)	0·323	1·039 (0·979–1·103)	0·206	0·935 (0·882–0·991)	0·023	0·996 (0·919–1·079)	0·916	0·867 (0·715–1·052)	0·148
DLCO (per 5-unit change)	0·89 (0·82–0·965)	0·005	0·705 (0·543–0·915)	0·009	0·844 (0·771–0·923)	<0·0001	0·86 (0·79–0·937)	0·001	0·749 (0·657–0·853)	0·0002	0·696 (0·508–0·953)	0·024
6MWD (per 5-unit change)	1·003 (0·994–1·011)	0·557	0·978 (0·959–0·998)	0·028	0·983 (0·974–0·991)	<0·0001	1·005 (0·997–1·014)	0·224	0·993 (0·981–1·004)	0·202	0·971 (0·947–0·996)	0·026
UCSD-SOBQ (per 5-unit change)	1·011 (0·979–1·045)	0·498	1·042 (0·967–1·124)	0·281	0·996 (0·96–1·033)	0·821	1·03 (0·997–1·065)	0·074	1·052 (1·005–1·102)	0·031	0·958 (0·868–1·058)	0·396
Comorbidities												
Cardiovascular disease	1·0 (0·8–1·4)	0·869	1·7 (0·9–3·4)	0·133	0·9 (0·7–1·3)	0·628	1·1 (0·8–1·5)	0·538	1·7 (1·1–2·5)	0·014	1·8 (0·8–4·2)	0·179
Chronic respiratory failure	1·8 (1–3·2)	0·069	1·8 (0·5–6·2)	0·351	1·7 (0·8–3·6)	0·146	1·2 (0·6–2·3)	0·588	1·4 (0·6–3·4)	0·404	2·9 (0·8–10·4)	0·103
COPD	1·5 (0·8–2·7)	0·231	1·3 (0·3–5·5)	0·738	0·8 (0·4–1·9)	0·626	1·3 (0·7–2·5)	0·348	1·4 (0·6–3·2)	0·484	0·8 (0·1–6·7)	0·873
Sleep apnoea	1·4 (0·9–2)	0·095	0·6 (0·2–1·7)	0·310	1·2 (0·8–1·8)	0·449	1·3 (0·9–1·9)	0·138	1·0 (0·6–1·6)	0·881	0·7 (0·2–2·6)	0·627
Gastrointestinal comorbidities												
GERD	1·0 (0·7–1·3)	0·801	1·5 (0·7–3·4)	0·333	1·0 (0·7–1·5)	0·835	1·0 (0·7–1·5)	0·809	1·5 (0·9–2·5)	0·099	1·7 (0·7–4·6)	0·253
Hiatus hernia	1·5 (1–2·3)	0·069	0·9 (0·3–2·7)	0·867	0·8 (0·4–1·3)	0·294	1·6 (1–2·4)	0·034	1·0 (0·5–1·7)	0·891	1·7 (0·5–5·4)	0·379
Barrett's oesophagus	0·3 (0–2·4)	0·265	..	..	..	..	0·3 (0–2)	0·209	2·5 (0·6–10·7)	0·231	..	..
HP-positive gastritis†	..	..	..	..	..	..	..	..	..	..	..	..
Cardiovascular risk factors												
Hypertension	1·3 (0·9–1·8)	0·110	0·8 (0·4–1·6)	0·480	1·0 (0·7–1·5)	0·895	1·3 (1–1·8)	0·069	1·3 (0·8–2)	0·263	0·8 (0·3–2)	0·581
Diabetes	0·9 (0·6–1·1)	0·279	0·9 (0·5–1·8)	0·755	0·8 (0·6–1·2)	0·285	0·9 (0·7–1·2)	0·536	0·7 (0·5–1·1)	0·087	1·0 (0·4–2·3)	0·985
Hypercholesterolaemia	0·9 (0·7–1·2)	0·442	0·7 (0·3–1·4)	0·293	0·7 (0·5–1)	0·043	1·1 (0·8–1·5)	0·412	0·9 (0·6–1·4)	0·762	0·6 (0·3–1·5)	0·281
Obesity	0·9 (0·7–1·2)	0·404	1·1 (0·6–1·9)	0·853	1·0 (0·8–1·3)	0·996	0·9 (0·7–1·2)	0·407	1·5 (1–2·1)	0·043	0·8 (0·4–1·6)	0·464

FVC=forced vital capacity. 6MWD=6 min walk distance. IPF=idiopathic pulmonary fibrosis. DLCO=haemoglobin-corrected predicted diffusing capacity of the lung for carbon monoxide. UCSD-SOBQ=University of California at San Diego Shortness of Breath Questionnaire. COPD=chronic obstructive pulmonary disease. GERD=gastro-oesophageal reflux disease. HP=*Helicobacter pylori*. *Only all-cause hospital admission was run with death as a competing risk. †Too few patients were available to analyse for HP-positive gastritis.

Table 5: **Unadjusted and adjusted analyses**

not receive antacid therapy (p=0·7971); similarly, in patients with percentage-predicted FVC of 70% or more, the rates did not differ (51 [35%] *vs* 66 [39%]; p=0·4528). Furthermore, changes in FVC, 6MWD, and all-cause hospital admission did not differ between the antacid therapy groups when the patients were stratified by baseline FVC. Similar results were obtained when baseline FVC was stratified by 60% or more versus less than 60% (data not shown).

When assessed in adjusted analysis using a shared frailty model, antacid therapy was not associated with progression-free survival, any of the components of the progression-free survival composite score, all-cause hospital admission, or IPF-related mortality (table 5).

Patients who received antacid therapy had similar rates of all-cause hospital admission, gastrointestinal adverse effects, infections, and pulmonary infections compared with patients who did not receive antacid therapy (table 3). When patients were stratified by baseline FVC, gastrointestinal adverse effects were similar irrespective of antacid therapy use. However, in patients with a predicted FVC of less than 70%, infections were significantly higher with antacid therapy use than with no antacid therapy use (107 [74%] *vs* 101 [62%]; p=0·0174). Similar differences were also seen for pulmonary infection rates (20 [14%] *vs* 10 [6%]; p=0·0214).

Discussion

In this post-hoc analysis of patients with IPF randomly assigned to placebo in three large controlled trials, antacid therapy did not yield clinically significant improvements in outcomes after 52 weeks. We found no association between antacid therapy and progression-free survival, mortality, or adverse events. Patients with advanced IPF (<70% FVC) who received antacid therapy had similar rates of progression-free survival and mortality, but had higher infection rates (both pulmonary and non-pulmonary) than patients who did not receive antacid therapy.

Antacid therapy has been given a conditional recommendation for use in the 2015 IPF treatment guidelines,[16] which is unchanged from the 2011 guidelines. Retrospective analyses have reported that patients who received antacid therapy had slower disease progression, as assessed by decrease in FVC, and improved survival compared with patients who did not receive antacid therapy.[11,17] In an analysis of the placebo groups of three randomised controlled trials of patients with IPF, antacid therapy use was associated with a significantly smaller decrease in FVC compared with no antacid use, although no differences were reported for all-cause mortality or all-cause hospital admission.[17] Fewer acute exacerbations were also reported in patients who receive antacid therapy than in those who did not received antacid therapy. Additional studies suggested that antacid therapy helped stabilise IPF.[21]

By contrast with the findings of previous studies, our findings do not support any beneficial effect of antacid therapy in patients with IPF. We did multiple sensitivity analyses using stratification by FVC of less than 70% versus FVC of 70% or more and by antacid therapy use in patients with gastro-oesophageal reflux disease only, and saw similar results to our main analysis (data not shown). One explanation for the difference in findings from previous studies could be related to differences in patient characteristics. In the phase 3 CAPACITY and ASCEND trials,[2,3] few patients had advanced disease, as assessed by functional impairment. Patients awaiting lung transplantation were also excluded, and antacid therapy might potentially benefit this patient population.[22] In the IPFnet-sponsored trials,[17] mean baseline percentage of predicted FVC was about 59% in STEP-IPF, about 58·5% in ACE-IPF, and about 71% in PANTHER compared with about 75% in CAPACITY and about 68% in ASCEND.[2,3] Although some studies have suggested that gastro-oesophageal reflux disease is more prevalent in patients with advanced IPF, our data analysis of patients stratified on the basis of their FVC being less than 70% or 70% or more did not show a significant difference in terms of effects by antacid therapy. Because the IPFnet-sponsored studies were not analysed separately, it is impossible to ascertain whether STEP-IPF, which included patients with advanced IPF, contributed the most to the results. However, with regard to the retrospective analysis[11] suggesting that antacid therapy might confer a survival benefit, diagnosis of gastro-oesophageal reflux disease in patients with IPF might introduce a lead-time bias, thus accounting for the better prognosis associated with antacid therapy use than with no antacid therapy use. Furthermore, different follow-up times (eg, 30 weeks in the IPFnet study and 52 weeks in our study) could have contributed to different results. Although comorbidities, such as cardiovascular disease and sleep apnoea, were more prevalent in patients who received antacid therapy and could have affected the results, disease progression and survival analyses were adjusted for comorbidities and no association was seen in these models.

In this analysis, although the overall cohort had no significant differences between groups, patients with advanced IPF (eg, FVC <70%) who received antacid therapy had a significantly higher incidence of infections, both pulmonary and non-pulmonary, than those who did not receive the treatment, which is consistent with previous studies reporting a higher incidence of ventilator-associated and community-acquired pneumonias in patients given antacid therapy versus those not given the treatment.[23,24] Baseline FVC of less than 70% was chosen because it was the mean FVC of the patient population and allowed for fair statistical evaluations in sufficiently large subgroups of patients. For patients with an FVC of less than 60%, similar results were recorded (data not shown). Because of their retrospective nature and non-randomised comparisons, results should be interpreted with caution. Moreover, we note that because of a relatively small sample size, these analyses were probably underpowered to detect meaningful differences. Along the lines of increased infections, the data from a co-trimoxazole trial[25] in IPF are noteworthy. In a double-blind multicentre study,[25] patients with IPF who received co-trimoxazole treatment had no differences in pulmonary function outcomes compared with placebo; however, a significant reduction in all-cause mortality was associated with reduction in the rate of respiratory tract infections.

A personalised treatment approach to patients with IPF receiving antacid therapy, especially those with advanced disease, might be needed to mitigate infections. Additionally, a retrospective study[26] reported that, in patients with IPF and hiatus hernia, but not in those without hernia, antacid therapy use was associated with preserving DLCO, suggesting that an individualised approach could be beneficial.[26] Perhaps a formal test for gastro-oesophageal reflux disease is needed before administration of antacid therapy in patients with IPF.

Our study has several limitations. It was a post-hoc analysis from randomised controlled trials. Although we used prospectively collected data, the study population was not randomised for antacid therapy or stratified for imbalances in comorbidities; although our adjusted analysis addressed this potential bias, it was only for differences between groups in observed factors. We note that a formal power analysis was not done and as such we cannot exclude the possibility that the study was not powered adequately to address this question fully. Additionally, patients with advanced disease and those listed for lung transplantation (ie, FVC <50%), who could potentially benefit the most from antacid therapy, were not included in the ASCEND and CAPACITY trials. Furthermore, the observation time was limited to 52 weeks because of a substantially decreasing patient population as the ASCEND trial was done only until week 52. We cannot rule out that a longer duration of antacid therapy might have had a positive effect on the course of the disease and that other risk factors might have been identified. Additionally, some patients initiated or discontinued antacid therapy during the trial after their baseline assessment. Although results from analyses including antacid therapy as a time-dependent variable were largely the same as our base-case analyses, they did suggest that antacid therapy might be associated with a reduced risk of mortality (data not shown). However, we believe that these analyses might be biased because a large percentage of deaths occurred after treatment discontinuation, and discontinuation probably occurred because of disease progression that ultimately led to death (and not because patients were no longer receiving antacid therapy).

Our study does not support a previously reported association between antacid therapy and reduced IPF disease progression. Although clinicians might reasonably offer antacid therapy to patients with IPF who have symptomatic gastro-oesophageal reflux or offer fundoplication to those with uncontrolled reflux symptoms, our data do not suggest that antacids are beneficial as a treatment for IPF. Furthermore, our data highlight the possibility that individuals with advanced disease might actually be at an increased risk of infections when given antacid therapy. Long-term double-blind randomised studies are urgently needed to further investigate the potential benefit (and possible harms) of antacid therapy in patients with different stages of IPF, especially those with advanced disease.

Contributors

MKr, WW, DW, PS, and UC were involved in the study design. DW did the statistical analyses. MKr, WW, ER, DK, TMM, MKo, PS, K-UK, FJFH, and UC contributed to data collection, analysis, and interpretation.

Declaration of interests

MKr reports grants and personal fees from Boehringer Ingelheim and InterMune/Roche, during the conduct of the study. PS reports personal fees from Boehringer Ingelheim, Intermune/Roche/Genentech, Chiesi Farmaceutici, and Santhera Pharmaceuticals, outside of the submitted work; and PS's wife is an employee of Novartis. DK reports personal fees from Intermune/Roche and Boehringer Ingelheim. TMM declares no interests directly related to this manuscript; however, he has received industry-academic research funding from GlaxoSmithKline research and development, UCB, and Novartis, and has received consultancy or speakers fees from Apellis Bayer, Biogen Idec, Boehringer Ingelheim, Dosa, GlaxoSmithKline research and development, ProMetic, Roche, Sanofi-Aventis, and UCB. MKo reports grants from Intermune/Roche Canada, during the conduct of the study; grants and personal fees from Roche and Boehringer Ingelheim, personal fees from GlaxoSmithKline, AstraZeneca, Gilead, Prometic, and Genoa; and grants from Actelion and Respivert, outside of the submitted work. ER reports personal fees from Roche, Boeringher, Takeda, and Intermune/Roche, outside of the submitted work. UC reports grants, personal fees, and non-financial support from Boehringer, Intermune/Roche; and personal fees from Roche, Bayer, Gilead, GlaxoSmithKline, and Centocor, outside of the submitted work. DW is employed by PAI Inc and reports funding from F Hoffmann-La Roche, during the conduct of the study. WW reports grants from Intermune/Roche and personal fees from Boehringer Ingelheim, Roche, and Bayer, outside of the submitted work. K-UK is an employee of F Hoffmann-La Roche. FJFH declares no competing interests.

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