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Statin Therapy and Outcomes in Trials of Nintedanib in Idiopathic Pulmonary Fibrosis

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Keywords
Interstitial lung diseases · Cardiovascular diseases · Comorbidity · Forced vital capacity

Abstract
Background: Cardiovascular comorbidities are frequent in patients with idiopathic pulmonary fibrosis (IPF), and many patients with IPF receive treatment with statins to reduce cardiovascular risk. ***Objectives:*** We investigated whether statin use at baseline was associated with differences in disease progression in placebo-treated patients or influenced the treatment effect of nintedanib in the INPULSIS® trials. ***Methods:*** Post-hoc subgroup analyses of patients receiving versus not receiving statins at baseline using pooled data from the INPULSIS® trials. ***Results:*** At baseline, 312 patients received statins and 749 did not. The annual rates of decline in forced vital capacity (FVC) in patients treated with nintedanib and placebo, respectively, were –78.9 and –187.6 mL/year in patients who received statins at baseline, and –127.9 and –237.9 mL/year in patients who did not. The effect of nintedanib was consistent across subgroups (p = 0.9590). ***Conclusions:*** In the INPULSIS® trials, there was a numerically lower FVC decline in placebo-treated patients with IPF who received statins at baseline versus those who did not. Use of statins at baseline did not influence the treatment effect of nintedanib. Prospective data are needed to assess the impact of statins on the course of IPF.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a specific form of interstitial lung disease (ILD) characterised by progressive decline in lung function, worsening dyspnoea, and

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impaired health-related quality of life [1, 2]. The pathogenesis of IPF is believed to involve epithelial injury and impaired wound healing. Alveolar epithelial cells secrete pro-fibrotic growth factors, which stimulate the proliferation and migration of fibroblasts and myofibroblasts, leading to excessive secretion of extracellular matrix and remodelling of the lung architecture [3, 4].

IPF is more common in men than women, more common in people with a history of smoking, and typically presents in the sixth or seventh decade of life [1]. Cardiovascular diseases are common comorbidities in patients with IPF [5–8] and many patients with IPF are receiving medications to reduce cardiovascular risk such as statins to treat hypercholesterolaemia [9]. In addition to their lipid-lowering properties, statins have anti-inflammatory and antioxidant effects [10–12], and decrease senescence-associated secretory phenotypes that may be involved in the pathogenesis of IPF [13, 14]. Furthermore, non-clinical studies have demonstrated that statins have inhibitory effects on mediators of fibrosis, including connective tissue growth factor, transforming growth factor-β_1 and α-smooth muscle actin, induce fibroblast apoptosis, and reduce epithelial-mesenchymal transition in lung fibroblasts and alveolar epithelial cells from patients with IPF [15–18].

Data on the effect of statins on the development and progression of ILD are conflicting. A systematic review of published case reports and data from the US Food and Drug Administration adverse events database suggested a link between statin use and the development of ILD [19]. Statin use was associated with interstitial lung abnormalities in a large cohort of smokers participating in the COPDGene study [20]. Conversely, among elderly men participating in the observational Normative Aging Study, lung function decline was lower in those who used statins [21]. In addition, no association between use of statins and risk of ILD was observed within a large population-based cohort of users of respiratory medications between 1990 and 2005 [22]. Data from a retrospective single-centre study of 478 patients with IPF suggested no effect of statins on survival over a 3-year period [23], while an analysis of data from Danish patients with IPF who were followed for a median of 2.5 years demonstrated lower mortality in patients who were treated with statins, after adjusting for the presence of cardiovascular disease and diabetes [24]. Recently, a post hoc analysis of 624 patients with IPF who received placebo in three trials of pirfenidone suggested that use of statin therapy at baseline may be associated with a lower risk of IPF-related death or hospitalisation over 1 year of follow-up [25]. Prior to the present study, no data had been published on the potential impact of statin therapy on the treatment effects of anti-fibrotic therapies in patients with IPF.

Nintedanib is an intracellular inhibitor of tyrosine kinases [26] that has been approved for the treatment of IPF in several countries and regions, including the US, Europe, and Japan [27, 28]. The efficacy and safety of nintedanib 150 mg twice daily (b.i.d.) were investigated in the two replicate Phase III INPULSIS® trials [29]. Compared with placebo, nintedanib significantly reduced disease progression by reducing the annual rate of decline in forced vital capacity (FVC), with consistent treatment effects observed across subgroups defined by a variety of baseline characteristics including the use of corticosteroids [30] and anti-acid medications [31]. Investigator-reported acute exacerbations were reduced with nintedanib in INPULSIS®-2, but not in INPULSIS®-1. Gastrointestinal adverse events, particularly diarrhoea, were the most frequent adverse events in the nintedanib group.

Using pooled data from the INPULSIS® trials, we investigated whether statin use at baseline was associated with differences in the natural course of disease in patients with IPF who received placebo or influenced the treatment effect of nintedanib.

Methods

The design of the INPULSIS® trials has been described [29, 32]. In brief, participants had IPF diagnosed within the previous 5 years, FVC ≥50% predicted and a diffusing capacity of the lungs for carbon monoxide (DLco) 30–79% predicted. Patients were randomised (3:2) to nintedanib 150 mg b.i.d. or placebo for 52 weeks, with a follow-up visit 4 weeks later. The clinical trial protocol was approved by an Independent Ethics Committee and/or Institutional Review Board at all the participating centres.

Post hoc subgroup analyses were conducted using pooled data from the two INPULSIS® trials. Analyses were based on patients who received ≥1 dose of study drug. Statins were defined according to Anatomical Therapeutic Chemical 3 coding (online supplement; see www.karger.com/doi/10.1159/000486286 for all online suppl. material). Patients who started a statin before the first intake of trial medication and did not stop it until after the first intake of trial medication were defined as using statins at baseline.

To investigate whether statin use at baseline was associated with differences in the natural course of disease, analyses of the annual rate of decline in FVC, time to first investigator-reported acute exacerbation, change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score, time to absolute decline in FVC ≥5% predicted or death, or FVC ≥10% predicted or death, over 52 weeks, were conducted in patients treated with placebo. Time to an absolute decline in FVC ≥5% predicted or death, or FVC ≥10% predicted or death, over 52 weeks, was assessed using a Cox regression model. The original statistical approach was repeated for each endpoint with treatment replaced by baseline

Table 1. Baseline characteristics by subgroup

	Statins at baseline			No statins at baseline		
	nintedanib (*n* = 192)	placebo (*n* = 120)	total (*n* = 312)	nintedanib (*n* = 446)	placebo (*n* = 303)	total (*n* = 749)
Age, years	67.7±7.4	70.1±6.3	68.6±7.1	66.1±8.4	65.7±8.1	66.0±8.3
Male	152 (79.2)	97 (80.8)	249 (79.8)	355 (79.6)	237 (78.2)	592 (79.0)
Race						
White	129 (67.2)	88 (73.3)	217 (69.6)	231 (51.8)	160 (52.8)	391 (52.2)
Asian	38 (19.8)	19 (15.8)	57 (18.3)	156 (35.0)	109 (36.0)	265 (35.4)
Black	1 (0.5)	0	1 (0.3)	1 (0.2)	0	1 (0.1)
Missing[a]	24 (12.5)	13 (10.8)	37 (11.9)	58 (13.0)	34 (11.2)	92 (12.3)
Centrilobular emphysema[b]	71 (37.0)	49 (40.8)	120 (38.5)	183 (41.0)	117 (38.6)	300 (40.1)
FVC, mL	2,726±763	2,759±791	2,739±773	2,708±755	2,715±819	2,711±781
FVC, % predicted	80.8±17.9	81.3±19.5	81.0±18.5	79.3±17.4	78.5±17.7	79.0±17.5
FEV_1/FVC, %	81.6±6.0	80.9±5.3	81.3±5.7	81.7±5.8	82.0±6.2	81.8±5.9
DLco, % predicted	49.5±15.4	47.8±13.1	48.9±14.6	46.5±12.5	46.6±13.5	46.6±12.9
SGRQ, total score[c]	40.4±19.0	37.8±17.2	39.4±18.3	39.1±19.2	40.3±19.0	39.6±19.1
Cardiovascular risk factors[d]						
Former or current smoker	148 (77.1)	90 (75.0)	238 (76.3)	316 (70.9)	211 (69.6)	527 (70.4)
Hypertension	121 (63.0)	83 (69.2)	204 (65.4)	155 (34.8)	91 (30.0)	246 (32.8)
Hypercholesterolaemia	74 (38.5)	55 (45.8)	129 (41.3)	13 (2.9)	16 (5.3)	29 (3.9)
Diabetes	33 (17.2)	24 (20.0)	57 (18.3)	55 (12.3)	25 (8.3)	80 (10.7)
Hyperlipidaemia	64 (33.3)	31 (25.8)	95 (30.4)	22 (4.9)	7 (2.3)	29 (3.9)
Obesity	12 (6.3)	11 (9.2)	23 (7.4)	23 (5.2)	13 (4.3)	36 (4.8)
Cardiac disorders[e]						
Coronary artery disease	30 (15.6)	35 (29.2)	65 (20.8)	15 (3.4)	8 (2.6)	23 (3.1)
Myocardial infarction	18 (9.4)	8 (6.7)	26 (8.3)	7 (1.6)	4 (1.3)	11 (1.5)
Myocardial ischaemia	17 (8.9)	4 (3.3)	21 (6.7)	4 (0.9)	4 (1.3)	8 (1.1)
Angina pectoris	15 (7.8)	6 (5.0)	21 (6.7)	3 (0.7)	0 (0.0)	3 (0.4)

Data are presented as mean ± standard deviation or *n* (%). DLco, diffusing capacity of the lungs for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity. [a] In France, regulation did not permit the collection of data on race. [b] Based on qualitative assessment of high-resolution computed tomography scans. [c] *n* = 187 for nintedanib, *n* = 118 for placebo in statins subgroup; *n* = 437 for nintedanib, *n* = 301 for placebo in no statins subgroup. [d] By Medical Dictionary for Regulatory Activities preferred term (except for smoking status). [e] Reported in ≥5% of patients in any of the four subgroups, by Medical Dictionary for Regulatory Activities preferred term.

statin use as an effect, or part of an interaction effect, in the model where relevant.

To investigate the potential influence of statin use at baseline on the treatment effect of nintedanib, analyses of these endpoints were conducted within each subgroup. For the annual rate of decline in FVC, the term subgroup and the interaction terms treatment-by-baseline statin use, time-by-baseline statin use and treatment-by-time-by-baseline statin use were added to the original statistical model. For time to first investigator-reported acute exacerbation and change from baseline in SGRQ total score, over 52 weeks, a baseline statin use term and a treatment-by-baseline statin use interaction term were added to the model. Time to an absolute decline in FVC ≥5% predicted or death, or an absolute decline in FVC ≥10% predicted or death, over 52 weeks, was assessed using a Cox regression model with a baseline statin use term and a treatment-by-baseline statin use interaction term added to the model.

Acute exacerbations were defined as events meeting all of the following criteria: unexplained worsening or development of dyspnoea within 30 days; new diffuse pulmonary infiltrates on chest X-ray and/or high-resolution computed tomography parenchymal abnormalities with no pneumothorax or pleural effusion (new ground-glass opacities) since last visit; and exclusion of known causes of the acute worsening, as per routine clinical practice and microbiological studies.

Safety was assessed via clinical and laboratory evaluation and the recording of adverse events with onset after the first dose and up to 28 days after the last dose of study drug. Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 16.1. Myocardial infarction and other ischaemic heart disease were based on events in the subordinate standardised MedDRA queries (SMQs) "myocardial infarction" and "other ischemic heart disease." Major adverse cardiovascular

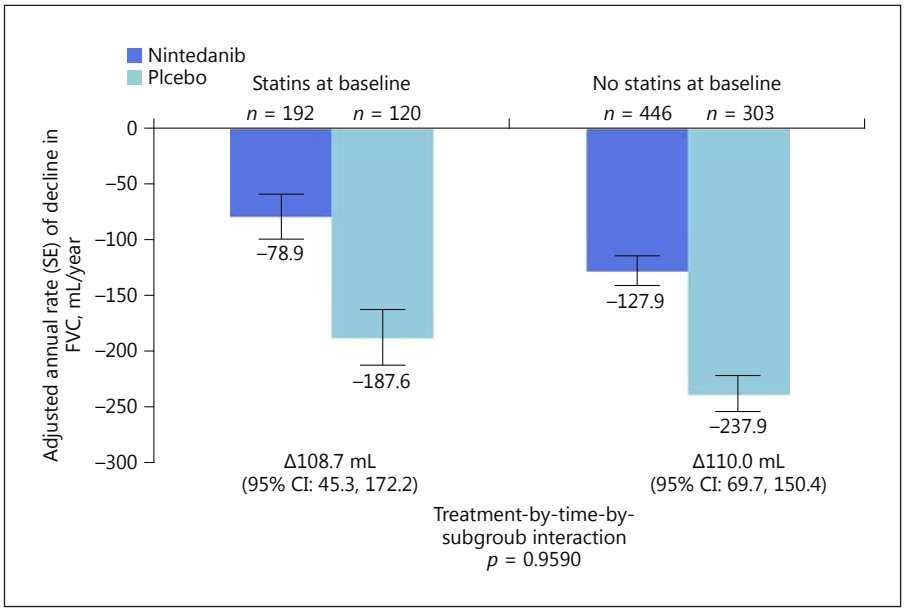

Fig. 1. Annual rate of decline in FVC by subgroup.

events were based on fatal adverse events included in the MedDRA system organ classes "cardiac disorders" and "vascular disorders"; events in the subordinate SMQ "myocardial infarction"; selected preferred terms from the subordinate SMQs "hemorrhagic cerebrovascular conditions" and "ischemic cerebrovascular conditions"; and the MedDRA preferred terms "sudden death," "cardiac death" and "sudden cardiac death." Safety analyses were descriptive.

Results

Patients

In total, 312 patients (29%) were receiving statins at baseline (192 in the nintedanib group, 120 in the placebo group) and 749 patients (71%) were not (446 in the nintedanib group, 303 in the placebo group). Baseline demographics and clinical characteristics were mostly similar between the subgroups, but patients taking statins were older, a higher proportion had cardiac disorders and cardiovascular risk factors, and a higher proportion was white (Table 1). Of patients receiving statins at baseline in the nintedanib and placebo groups, the most frequently used statins were simvastatin (33 and 31%, respectively), atorvastatin calcium (27% and 21%, respectively), and rosuvastatin calcium (15 and 22%, respectively) (online suppl. Table S1).

In patients receiving statins at baseline, mean (SD) duration of exposure to study medication was 10.0 (3.5) and 11.1 (2.7) months in the nintedanib and placebo groups, respectively. In patients not receiving statins at baseline, mean (SD) duration of exposure to study medication was 10.4 (3.3) and 10.7 (2.9) months in the nintedanib and placebo groups, respectively.

Annual Rate of Decline in FVC

In analyses to investigate whether there was a difference in the natural course of IPF by statin use at baseline in patients treated with placebo, the adjusted annual rate of decline in FVC was −187.4 mL/year in patients receiving statins at baseline and −238.1 mL/year in patients not receiving statins at baseline (difference of 50.8 mL/year [95% CI: −10.9, 112.5]; $p = 0.1065$).

In analyses to investigate the potential influence of statins on the treatment effect of nintedanib, the adjusted annual rates of decline in FVC were −78.9 mL/year in the nintedanib group and −187.6 mL/year in the placebo group (difference of 108.7 mL/year [95% CI: 45.3, 172.2]) in patients receiving statins at baseline and −127.9 mL/year in the nintedanib group and −237.9 mL/year in the placebo group (difference of 110.0 mL/year [95% CI: 69.7, 150.4]) in patients not receiving statins at baseline (Fig. 1). The treatment effect of nintedanib was consistent between patients receiving and not receiving statins at baseline (treatment-by-time-by-subgroup interaction $p = 0.9590$).

Disease Progression

In analyses to investigate whether statin use was associated with a difference in the natural course of IPF in patients treated with placebo, there was no significant dif-

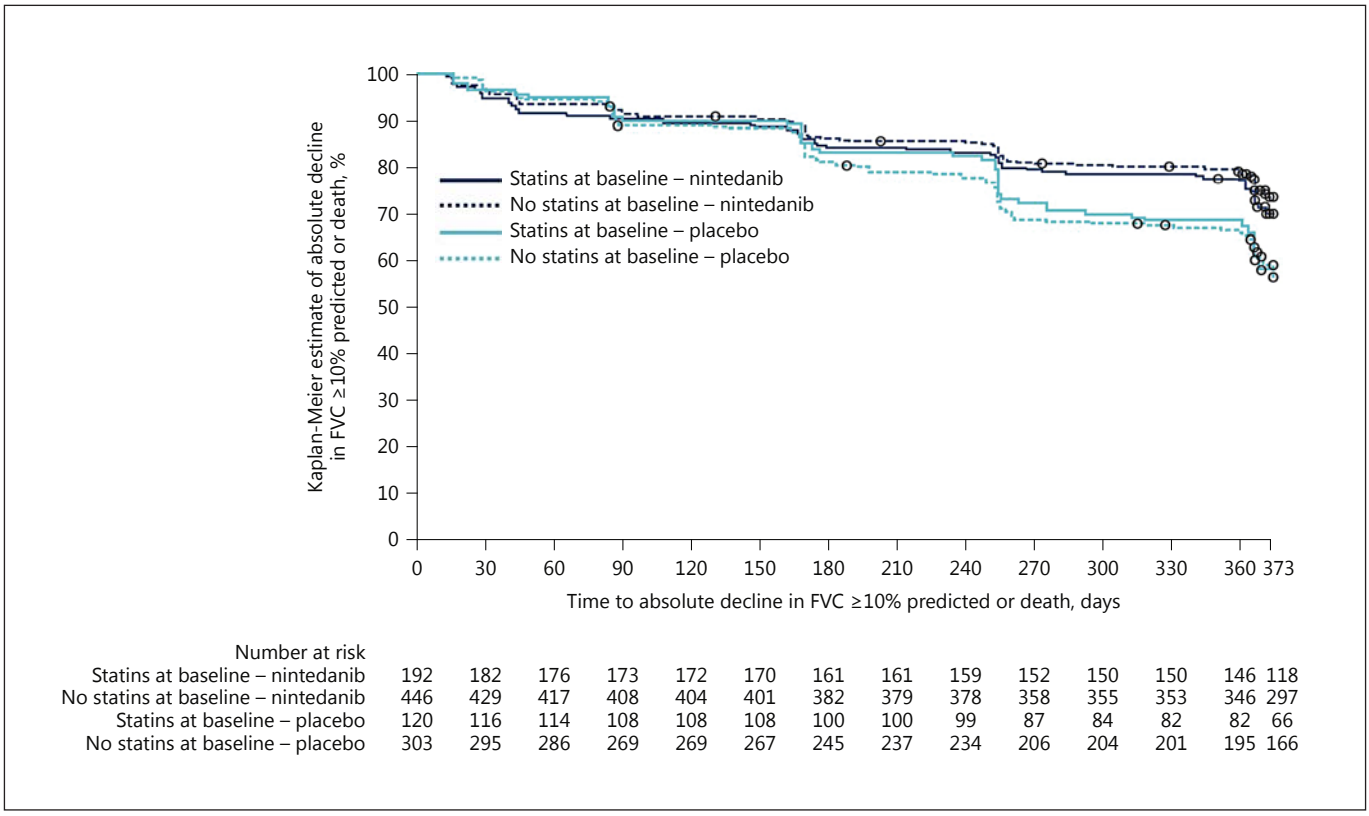

Fig. 2. Time to absolute decline in FVC ≥10% predicted or death by subgroup.

Table 2. Time to absolute decline in FVC ≥5% or death, or FVC ≥10% or death by subgroup

	Statins at baseline		No statins at baseline	
	nintedanib (n = 192)	placebo (n = 120)	nintedanib (n = 446)	placebo (n = 303)
Absolute decline in FVC ≥10% predicted or death, n (%)	57 (29.7)	52 (43.3)	116 (26.0)	123 (40.6)
HR (95% CI)	0.66 (0.45, 0.98)		0.58 (0.45, 0.75)	
Treatment-by-subgroup interaction	0.5817			
Criterion reached first, n (%)				
Absolute decline in FVC ≥10% predicted	46 (24.0)	44 (36.7)	102 (22.9)	109 (36.0)
Death	11 (5.7)	8 (6.7)	14 (3.1)	14 (4.6)
Absolute decline in FVC ≥5% predicted or death, n (%)	101 (52.6)	80 (66.7)	229 (51.3)	223 (73.6)
HR (95% CI)	0.72 (0.53, 0.97)		0.57 (0.47, 0.68)	
Treatment-by-subgroup interaction	0.1871			
Criterion reached first, n (%)				
Absolute decline in FVC ≥5% predicted	94 (49.0)	75 (62.5)	223 (50.0)	217 (71.6)
Death	7 (3.6)	5 (4.2)	6 (1.3)	6 (2.0)

CI, confidence interval; FVC, forced vital capacity; HR, hazard ratio.

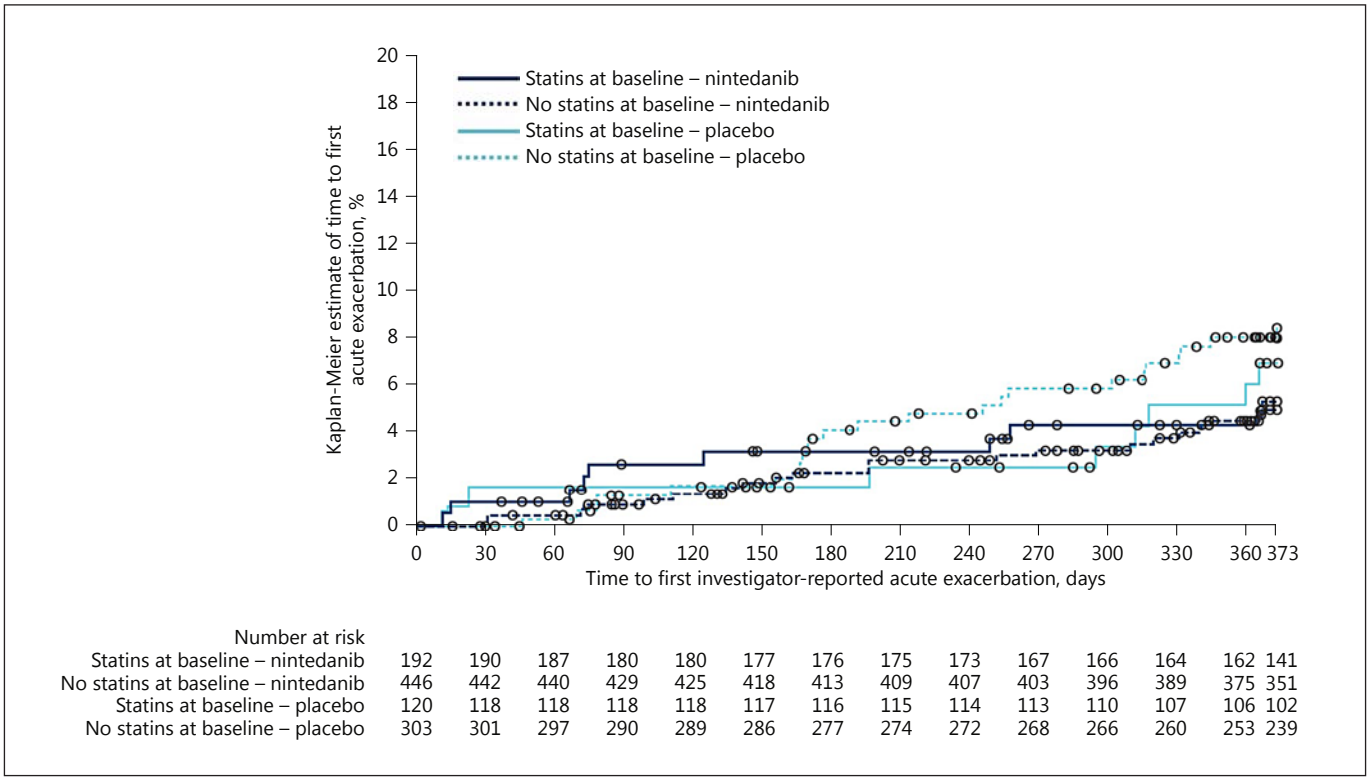

Fig. 3. Time to first acute exacerbation by subgroup.

ference in time to absolute decline FVC ≥5% predicted or death (HR 0.81 [95% CI: 0.62, 1.06]; $p = 0.1235$) or time to absolute decline FVC ≥10% predicted or death in patients receiving versus not receiving statins at baseline (HR 1.01 [95% CI: 0.72, 1.41]; $p = 0.9700$).

In analyses to investigate the potential influence of statins on the treatment effect of nintedanib, the HR for time to absolute decline in FVC ≥5% predicted or death was 0.72 (95% CI: 0.53, 0.97) in patients receiving statins at baseline and 0.57 (95% CI: 0.47, 0.68) in patients not receiving statins at baseline, both in favour of nintedanib. The treatment-by-subgroup interaction did not clearly suggest a differential treatment effect of nintedanib between the subgroups by statin use ($p = 0.1871$). The HR for time to absolute decline in FVC ≥10% predicted or death was 0.66 (95% CI: 0.45, 0.98) in patients receiving statins at baseline and 0.58 (95% CI: 0.45, 0.75) in patients not receiving statins at baseline, both in favour of nintedanib (Fig. 2). The treatment effect of nintedanib was consistent between the subgroups by statin use (treatment-by-subgroup interaction $p = 0.5817$). Most patients who met these endpoints for disease progression did so due to FVC decline rather than death (Table 2).

Acute Exacerbations of IPF

In analyses to investigate whether statin use was associated with a difference in the natural course of IPF in patients treated with placebo, there was no significant difference in time to first acute exacerbation in patients receiving versus not receiving statins at baseline (HR 0.76 [95% CI: 0.33, 1.73]; $p = 0.5144$).

In analyses to investigate the potential influence of statins on the treatment effect of nintedanib, the HR for time to first acute exacerbation was 0.67 (95% CI: 0.25, 1.80) in patients receiving statins at baseline (with acute exacerbations reported in 9 patients [4.7%] vs. 8 patients [6.7%]) and 0.60 (95% CI: 0.34, 1.08) in patients not receiving statins at baseline (with acute exacerbations reported in 22 patients [4.9%] vs. 24 patients [7.9%]), both in favour of nintedanib (Fig. 3). The treatment effect of nintedanib was consistent between the subgroups by statin use at baseline (treatment-by-subgroup interaction $p = 0.5926$).

SGRQ Total Score

In analyses to investigate whether statin use was associated with a difference in the natural course of IPF in patients treated with placebo, the adjusted mean change

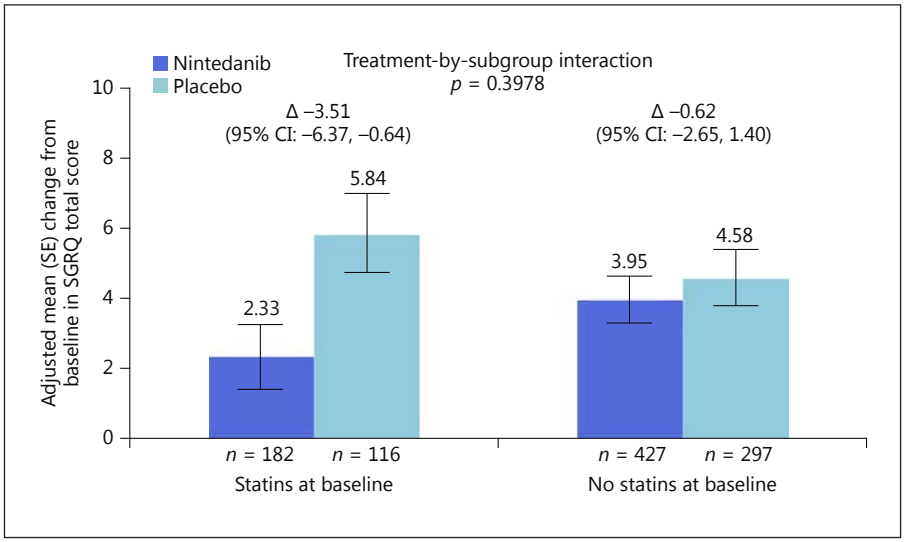

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Fig. 4. Change from baseline in SGRQ total score by subgroup.

from baseline in SGRQ total score over 52 weeks was 5.84 in patients receiving statins and 4.62 in patients not receiving statins at baseline (difference of 1.22 [95% CI: –1.65, 4.09]; $p = 0.4039$).

In analyses to investigate the potential influence of statins on the treatment effect of nintedanib, the adjusted mean change from baseline in SGRQ total score over 52 weeks was 2.33 in the nintedanib group and 5.84 in the placebo group (difference of –3.51 [95% CI: –6.37, –0.64]) in patients receiving statins at baseline and was 3.95 in the nintedanib group and 4.58 in the placebo group (difference of –0.62 [95% CI: –2.65, 1.40]) in patients not receiving statin at baseline (Fig. 4). The treatment effect of nintedanib was consistent between the subgroups by statin use at baseline (treatment-by-subgroup interaction $p = 0.3978$).

Adverse Events

A summary of adverse events by subgroup is presented in Table 3. Diarrhoea was the most frequent adverse event in patients treated with nintedanib, reported in 69.3 and 59.4% of patients receiving and not receiving statins at baseline, compared with 21.7 and 17.2% of placebo-treated patients in these subgroups, respectively. Diarrhoea led to permanent discontinuation of nintedanib in 6.3 and 3.6% of patients receiving and not receiving statins at baseline versus no and 0.3% of placebo-treated patients in these subgroups, respectively.

The proportions of patients who had major adverse cardiovascular events, ischaemic heart disease and myocardial infarction by subgroup are presented in Table 4. In patients receiving statins at baseline, major adverse cardiovascular events were reported in 4.7 and 3.3% of nintedanib- and placebo-treated patients, respectively. In patients not receiving statins, major adverse cardiovascular events were reported in 3.1 and 2.3% of nintedanib- and placebo-treated patients, respectively.

Discussion

In this post hoc analysis of pooled data from the INPULSIS® trials, the annual rate of decline in FVC was lower in placebo-treated patients who were receiving statins at baseline than in those who were not (–187.4 vs. –238.1 mL/year, respectively), but the difference between groups missed statistical significance ($p = 0.1065$). In placebo-treated patients, there was no difference in the time to decline in FVC ≥10% predicted or death between subgroups by use of statins at baseline. In a recent post hoc analysis of data from 624 patients with IPF treated with placebo in three trials of pirfenidone, there was a numerical but non-significant effect in favour of statin use at baseline on time to decline in FVC ≥10% predicted or death after 52 weeks (HR 0.71 [95% CI: 0.48, 1.07]; $p = 0.1032$) [25]. Among patients treated with placebo in our study, slightly fewer patients receiving versus not receiving statins at baseline had an investigator-reported acute exacerbation (6.7 vs. 7.9%), but these data should be interpreted with caution given the small number of events. Taken together, these data suggest that statins do not have a negative influence in patients with IPF and there is no

Table 3. Adverse events by subgroup

	Statins at baseline		No statins at baseline	
	nintedanib (*n* = 192)	placebo (*n* = 120)	nintedanib (*n* = 446)	placebo (*n* = 303)
Any adverse event(s)	184 (95.8)	108 (90.0)	425 (95.3)	271 (89.4)
Most frequent adverse event(s)[a]				
Diarrhoea	133 (69.3)	26 (21.7)	265 (59.4)	52 (17.2)
Nausea	55 (28.6)	7 (5.8)	101 (22.6)	21 (6.9)
Nasopharyngitis	19 (9.9)	17 (14.2)	68 (15.2)	51 (16.8)
Cough	26 (13.5)	19 (15.8)	59 (13.2)	38 (12.5)
Progression of IPF[b]	18 (9.4)	13 (10.8)	46 (10.3)	48 (15.8)
Bronchitis	22 (11.5)	10 (8.3)	45 (10.1)	35 (11.6)
Upper respiratory tract infection	18 (9.4)	11 (9.2)	40 (9.0)	31 (10.2)
Dyspnoea	16 (8.3)	15 (12.5)	33 (7.4)	33 (10.9)
Decreased appetite	28 (14.6)	8 (6.7)	40 (9.0)	16 (5.3)
Vomiting	29 (15.1)	1 (0.8)	45 (10.1)	10 (3.3)
Fatigue	16 (8.3)	12 (10.0)	24 (5.4)	21 (6.9)
Abdominal pain	25 (13.0)	4 (3.3)	31 (7.0)	6 (2.0)
Severe adverse event(s)[c]	50 (26.0)	31 (25.8)	124 (27.8)	68 (22.4)
Serious adverse event(s)[d]	54 (28.1)	43 (35.8)	140 (31.4)	84 (27.7)
Fatal adverse event(s)	16 (8.3)	10 (8.3)	21 (4.7)	21 (6.9)
Adverse event(s) leading to treatment discontinuation[e]	40 (20.8)	11 (9.2)	83 (18.6)	44 (14.5)
Diarrhoea	12 (6.3)	0 (0.0)	16 (3.6)	1 (0.3)
Progression of IPF[b]	3 (1.6)	3 (2.5)	10 (2.2)	18 (5.9)
Nausea	6 (3.1)	0 (0.0)	7 (1.6)	0 (0.0)
Pneumonia	3 (1.6)	0 (0.0)	3 (0.7)	1 (0.3)
Weight decreased	3 (1.6)	0 (0.0)	3 (0.7)	1 (0.3)

[a] Adverse events reported in ≥10% of patients in any of the four subgroups. [b] Corresponds to Medical Dictionary for Regulatory Activities term "IPF," which included disease worsening and acute exacerbations of IPF. [c] An event that was incapacitating or that caused an inability to work or to perform usual activities. [d] An event that resulted in death, was immediately life-threatening, resulted in persistent or clinically significant disability or incapacity, required or prolonged hospitalisation, was related to a congenital anomaly or birth defect, or was deemed serious for any other reason. [e] Adverse events leading to discontinuation in ≥1.5% of patients in any of the four subgroups.

Table 4. Adverse events of special interest

	Statins at baseline		No statins at baseline		All patients	
	nintedanib (*n* = 192)	placebo (*n* = 120)	nintedanib (*n* = 446)	placebo (*n* = 303)	nintedanib (*n* = 638)	placebo (*n* = 423)
Major adverse cardiovascular events[a]	9 (4.7)	4 (3.3)	14 (3.1)	7 (2.3)	23 (3.6)	11 (2.6)
Ischaemic heart disease[b]	11 (5.7)	2 (1.7)	16 (3.6)	15 (5.0)	27 (4.2)	17 (4.0)
Myocardial infarction[c]	4 (2.1)	1 (0.8)	6 (1.3)	1 (0.3)	10 (1.6)	2 (0.5)
Myocardial infarction	2 (1.0)	1 (0.8)	5 (1.1)	1 (0.3)	7 (1.1)	2 (0.5)
Acute myocardial infarction	2 (1.0)	0 (0.0)	1 (0.2)	0 (0.0)	3 (0.5)	0 (0.0)

[a] Based on fatal adverse events included in the system organ classes "cardiac disorders" and "vascular disorders" in the Medical Dictionary for Regulatory Activities (MedDRA); events in the subordinate standardised MedDRA query (SMQ) "myocardial infarction"; selected preferred terms from the subordinate SMQs "haemorrhagic cerebrovascular conditions" and "ischaemic cerebrovascular conditions"; and the MedDRA preferred terms "sudden death," "cardiac death," and "sudden cardiac death." [b] Based on SMQ "ischaemic heart disease." [c] Based on MedDRA preferred terms "myocardial infarction" and "acute myocardial infarction."

evidence to suggest that these drugs need to be discontinued. It remains unclear whether statin therapy has a positive effect on the clinical course of IPF; this could only be determined through a prospective randomised controlled trial.

Our analyses suggest that use of statins at baseline did not influence the treatment effect of nintedanib on lung function decline in patients with IPF. The effect of nintedanib on acute exacerbations of IPF was also consistent between the subgroups by statin use at baseline. Use of statins at baseline had no impact on change in SGRQ score in the placebo group (difference of 1.22 points [95% CI: –1.65, 4.09]; $p = 0.4039$). Although the treatment effect of nintedanib seemed to be more pronounced in the subgroup of patients receiving statins at baseline, the treatment-by-subgroup interaction did not suggest a differential treatment effect between subgroups. In addition, in the subgroup of patients receiving statins at baseline, mean SGRQ total score at baseline was higher in nintedanib-treated patients compared with placebo-treated patients, which might have influenced the treatment effect observed.

The adverse event profile of nintedanib in both subgroups was consistent with that observed in the overall patient population [29]. Diarrhoea adverse events occurred in a slightly higher proportion of patients who were receiving statins at baseline, consistent with the risk of gastrointestinal adverse events, including diarrhoea, acknowledged in the prescribing information for simvastatin and atorvastatin [33, 34]. In line with this finding, other gastrointestinal adverse events also seemed to be generally more frequent in nintedanib-treated patients who were receiving statins at baseline compared to nintedanib-treated patients who were not. As expected, patients receiving statins at baseline had a greater frequency of cardiac disorders and cardiovascular risk factors at baseline than patients not receiving statins. During the trials, a greater frequency of major adverse cardiovascular events was observed in patients who were receiving statins at baseline and in patients treated with nintedanib versus placebo. However, the overall number of patients with a major adverse cardiovascular event was generally low (34), and these findings should be interpreted with caution, particularly given the background incidence of ischaemic heart disease and myocardial infarction in patients with IPF [5, 6, 8], especially in those receiving statins.

These post hoc analyses have a number of limitations. As patients were not randomised by use of statins, no conclusions can be drawn from these data regarding causality of any effects observed. There were differences between the subgroups by statin use at baseline, such as age, comorbidities, CV risk factors, and race, which could have impacted on our findings. No data on actual statin use or changes in statin use prior to or during the trials were available. It is unclear whether any potential effect of statins is due to an effect on CV comorbidities or due to effects on the fibrotic process. The p values derived from these post hoc analyses were exploratory.

In conclusion, post hoc analyses of pooled data from the INPULSIS® trials showed a numerically lower FVC decline in placebo-treated patients who were receiving statins at baseline. Use of statins at baseline did not influence the treatment effect of nintedanib in patients with IPF. Future prospective studies to determine the possible effects of statins on the clinical course of IPF are needed.

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