Lung function improvement on triple modulators: high-resolution, nationwide data from the Danish Cystic Fibrosis Cohort

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Shareable abstract (@ERSpublications)
This nationwide real-world study uses high-resolution data to document that elexacaftor/tezacaftor/ivacaftor halts progression of lung disease in cystic fibrosis, and improves lung function across all ages, disease severities and prior modulator use https://bit.ly/3VsReh2

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Abstract

Background People living with cystic fibrosis in Denmark had early, universal access to triple modulator treatment with elexacaftor/tezacaftor/ivacaftor. Close monitoring allowed us to assess the impact of treatment on lung function and progression of lung disease in an unselected nationwide cystic fibrosis population from 6 years of age.

Methods Data were analysed using linear mixed-effect models to assess changes in levels and annual rates of change (slopes) in percent predicted (pp) forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and forced expiratory flow at 25–75% of FVC ($ppFEF_{25–75\%}$) between the 12 months pre-treatment and treatment periods. Subgroup analyses assessed the impact of elexacaftor/tezacaftor/ivacaftor among those with/without previous modulator treatment, normal/mild/moderate/severe lung disease at treatment initiation, children/adults and birth cohorts.

Results We included 392 people living with cystic fibrosis with a median (interquartile range) 12 (nine to 15) spirometry measurements per person. The mean (95% CI) improvement in $ppFEV_1$ was 13.0 (11.3–14.6) 12 months after initiation of elexacaftor/tezacaftor/ivacaftor treatment. The annual rate of change improved from −1.4 (−2.1 – −0.6) $ppFEV_1$ in the pre-treatment year to 2.7 (1.8–3.5) $ppFEV_1$ per year during treatment. Similarly, ppFVC increased by 8.0 (7.1–8.9) and $FEF_{25–75\%}$ by 19.5 (17.0–21.9).

Conclusions Using high-resolution data from a nationwide real-world setting, our study documents the impact of elexacaftor/tezacaftor/ivacaftor on lung function across subgroups based on age, disease severity and treatment history. These findings point towards a new period of consistent lung function improvement among people living with cystic fibrosis on elexacaftor/tezacaftor/ivacaftor.

Introduction

Cystic fibrosis (CF) is an autosomal recessive genetic disease, causing serious morbidity, including reduced lung function and premature mortality. The disease is caused by defects in the CF transmembrane

conductance regulator (CFTR) protein due to a mutated CFTR gene [1]. The most common and severe variant, F508del, is caused by loss of a phenylalanine at position 508 of the CFTR polypeptide [2]. The highest prevalence of F508del homozygosity is found in Northern and Central Europe. In Denmark, >90% of people with CF are carrying at least one F508del variant [3, 4].

Percent predicted forced expiratory volume in 1 s (ppFEV$_1$) is used globally in routine clinical practice to monitor lung disease progression, to assess treatment response, and to stratify disease stages in CF. Percent predicted forced vital capacity (ppFVC) and forced expiratory flow at 25–75% of FVC (ppFEF$_{25–75\%}$) are less commonly used in daily routine clinical practice of CF, but give an indication of lung volume and flow limitations in the small airways, respectively [5]. The ppFEF$_{25–75\%}$ is considered a marker of small airways disease, as it represents the peripheral airway regions that are more susceptible to inflammatory and remodelling processes [6].

Small-molecule CFTR modulator therapy has been a landmark discovery in the treatment of CF [7]. Randomised clinical trials have shown the efficacy of elexacaftor/tezacaftor/ivacaftor (ETI) on ppFEV$_1$ in both people with CF aged ⩾12 years with a mild-to-moderate reduction in lung function at baseline (ppFEV$_1$ 40–90), and in people with CF aged 6–11 years with a baseline ppFEV$_1$ >70 [8–12]. The effects of ETI obtained during routine clinical practice have been reported from a number of real-world settings, but most studies have not included all CF population groups, most often leaving out those with high lung function (ppFEV$_1$ ⩾90), children aged 6–11 years, certain comorbidities and solid organ transplantation [13–21]. The continued effects of ETI on progression of lung disease, beyond the immediate increase, has so far only been reported from a single study [22].

In this study, we present nationwide data from an unselected population of people with CF aged ⩾6 years in the Danish Cystic Fibrosis Cohort. People with CF were monitored closely before and after the national roll-out of ETI. Our objectives were to investigate the improvement in lung function levels assessed as ppFEV$_1$, ppFVC and ppFEF$_{25–75\%}$, as well as changes in the progression of lung disease assessed as annual rate of change (slopes) in lung function parameters by comparing the 12-month period before and 12 months after initiation of ETI treatment in people with CF aged ⩾6 years. In addition, we evaluated the response to ETI treatment in subpopulations defined by prior modulator treatment, lung disease severity at ETI initiation, paediatric *versus* adult populations and birth cohorts.

Methods

Study design and participants

The present study is part of the TransformCF study, which aims to assess the impact of ETI treatment on CF disease using data from routine clinical care. The study uses data from the Danish Cystic Fibrosis Cohort, which includes all people with CF in Denmark, Greenland and the Faroe Islands. In Denmark, ETI has been in use since May 2018, when the first few people with CF initiated treatment as part of clinical trials or compassionate-use programmes [8–10]. ETI became commercially available in Denmark for all people with CF aged ⩾12 years with at least one copy of the F508del variant in September 2020 and was immediately adopted as standard of care [23]. ETI subsequently became available for people with CF aged 6–11 years in February 2022.

This study includes all people with CF who initiated ETI at one of the two CF centres in Denmark between May 2018 and December 2022 and who had ⩾3 months of continuous ETI treatment. Data on lung function obtained within 21 days following ETI initiation were excluded from analysis to exclude measurements during the acute improvement of lung function in line with previous analysis of CFTR modulator effects [24]. The observation time included data until the end of 12 months treatment, death, discontinuation of treatment (defined as no ETI for ⩾3 months), or the end of the study period (28 March 2023). All people with CF provided written, informed consent to have their data included in the Danish CF Cohort. The database for the study was approved by the Danish Data Protection Agency (1-16-02-623-20).

Data collection and outcomes

Data collection followed a pre-specified protocol for clinical monitoring of people with CF initiating ETI in Denmark. People with CF were invited for monthly consultations at one of the two CF centres [25] and spirometry was performed routinely according to international recommendations [26] at all visits using Vyntus SPIRO spirometers (Vyaire, Chigago, IL, USA). All measurements used in the analysis were collected on in-clinic visits. The measured volumes were evaluated and stored using SentrySuite software (Vyaire). The ppFEV$_1$, ppFVC and ppFEF$_{25–75\%}$ values were generated based on sex-, height-, ethnicity- and age-specific references [27].

Information about demographic and clinical characteristics at ETI initiation were extracted from the Danish Cystic Fibrosis Cohort. These included data on age, sex, CF genotype, sweat chloride concentration, previous treatment with CFTR mono or dual modulators, chronic lung infections, pancreatic insufficiency and CF-related diabetes defined by insulin use. Weight and height were measured at all consultations, and body mass index (BMI; $kg \cdot m^{-2}$) was calculated. For people with CF aged <18 years, BMI z-scores were generated based on the World Health Organization (WHO) growth reference [28].

Data analysis

Data were analysed using R version 4.2.2 (R Core Team 2018). The primary outcome was change of $ppFEV_1$ assessed as the mean change in levels and slopes. The change in $ppFEV_1$ levels was assessed as the mean difference in $ppFEV_1$ at initiation of ETI and after 12 months ETI treatment based on model estimates. The change in FEV_1 slopes was assessed by comparing the annual rates of change in $ppFEV_1$ during the 12-month pre-treatment and treatment periods. Secondary outcomes were ppFVC and $ppFEF_{25–75\%}$, which were similarly assessed as change in levels and slopes.

Descriptive statistics were used to present characteristics of people with CF at ETI initiation as mean±SD or median (interquartile range (IQR)) for continuous variables, and as counts (%) for categorical variables. Piecewise linear mixed-effect models [29] were fitted to estimate changes in intercepts and slopes of $ppFEV_1$ between the pre-treatment and the treatment period. The model included the interaction between time (in days) from treatment initiation to $ppFEV_1$ measurement and a categorical variable encoding for pre-treatment and treatment periods. In addition, sex and age (in years) at ETI initiation were included as fixed effects. Participant- and centre-specific random intercepts were included to capture unexplained variation between individuals and centres, respectively. Different standard deviations were assumed in the pre-treatment and treatment periods for the mean-zero normally distributed random effects. When fitting the linear mixed model, fixed intercepts were initially used, followed by random intercepts and, lastly, random slopes. To avoid overfitting, the model with the lowest value of the Akaike information criterion (AIC) was chosen. A Gaussian serial correlation structure was assumed to capture dependencies between repeated measurements in the same individual [30, 31].

The analysis of the primary outcome, $ppFEV_1$, was repeated for subgroups defined by previous CFTR modulator treatment (treatment-naïve *versus* previously treated), severity of lung disease at initiation of ETI (severe: $ppFEV_1$ <40; moderate: $ppFEV_1$ ⩾40 to <70; mild: $ppFEV_1$ ⩾70 to <90; normal: $ppFEV_1$ ⩾90), child/adolescent or adult status at initiation of ETI (age <18 and ⩾18 years, respectively) and birth cohort (born in 1950–1979, 1980–1989, 1990–1999, 2000–2009 and 2010–2016). A similar model was used to estimate mean change in levels and slopes of the secondary outcomes, ppFVC and $ppFEF_{25–75\%}$. The analyses of secondary outcomes included subgroups defined by previous CFTR modulator treatment and child/adolescent or adult status at initiation of ETI. p-values <0.05 were considered statistically significant.

Results

Population characteristics

The Danish Cystic Fibrosis Cohort included 583 people with CF in the data collection period from 28 May 2017 to 28 March 2023. Of these, 413 initiated ETI treatment within the study period. Seven people with CF were excluded from analysis as they discontinued treatment within the first 3 months. Three of these were due to adverse effects. Another 14 people with CF were excluded from analysis because of missing lung function data (figure 1). Thus, analysis included a total of 392 people with CF initiating ETI in Denmark between 28 May 2018 and 22 December 2022. Background characteristics are provided in table 1. Most of the people with CF (73%) were homozygous for the F508del variant. The majority of people with CF (69%) were shifted to ETI from a prior generation CFTR modulator: 174 (44%) shifted from tezacaftor/ivacaftor, 93 (24%) from a lumacaftor/ivacaftor and five (1%) from ivacaftor monotherapy. Severity of lung disease at initiation of ETI was categorised as severe in 10%, moderate in 26% and mild in 29%, and 36% had lung function within the normal range. Among the study participants, 139 (35%) were children/adolescents, of whom 67 (17%) were aged 6–11 years at ETI initiation.

Lung function measurements

Among the people with CF, 362 (92%) had completed 12 months observation time on treatment. Three people with CF discontinued ETI before 12 months due to adverse effects; one died during the study period. The dataset included a total of 4949 unique spirometry test sessions. The number of measurements per person was similar between the pre-treatment and treatment period with a median (IQR) of six (five to eight) assessments before and six (four to eight) assessments after ETI initiation. Based on AIC values, a model with random intercepts but without random slopes was chosen for data analysis.

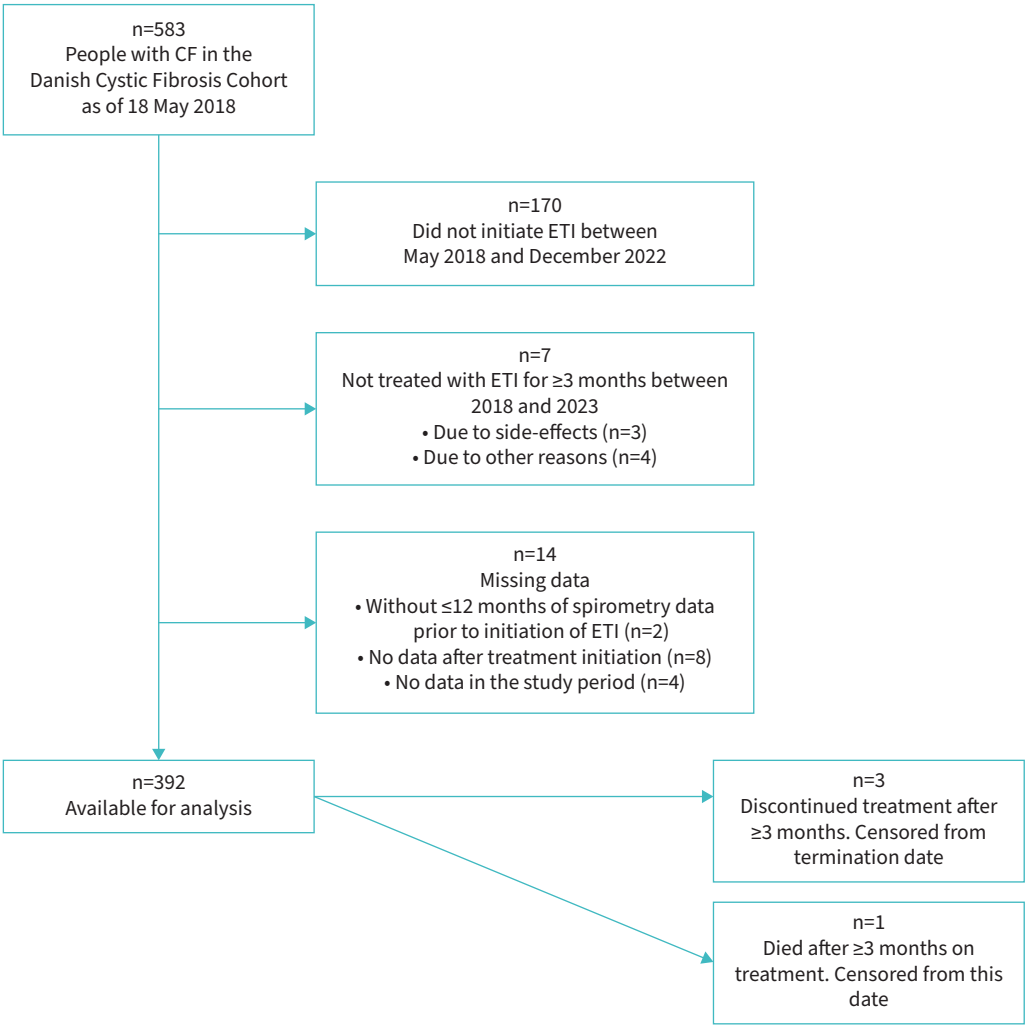

FIGURE 1 Selection of people with cystic fibrosis (CF) in the Danish Cystic Fibrosis Cohort for analysis. ETI: elexacaftor/tezacaftor/ivacaftor.

Change in levels of ppFEV$_1$

The mean (95% CI) ppFEV$_1$ at ETI initiation was 78.3 (76.2–80.3) and had increased by 13.0 (11.3–14.6) in the total population after 12 months of treatment (table 2, figure 2). The increase of ppFEV$_1$ was 12.1 (10.5–13.7) among people with CF previously treated with other CFTR modulators and 15.1 (13.0–17.2) among those without prior CFTR modulator treatment. The ppFEV$_1$ levels improved across all subgroups of lung disease severities, even among those starting with a normal lung function at ETI initiation: 8.0 (5.9–10.0). Among children/adolescents and adults, ppFEV$_1$ improved by 11.4 (9.8–13.1) and 13.9 (12.4–15.3), respectively, with similar improvement in ppFEV$_1$ extending across all birth cohorts.

Change in ppFEV$_1$ slopes

In the pre-treatment period, there was a negative annual rate of change in ppFEV$_1$ indicated by a slope of −1.4 (−2.1–−0.6) per year in the total people with CF population. After the initial improvement in level of ppFEV$_1$, lung function continued to improve during the treatment period with a positive slope of 2.7 (1.8–3.5) ppFEV$_1$ per year (table 3**,** figure 2). People with CF who had not previously been treated with earlier generations of CFTR modulators had a negative slope of −1.8 (−3.2–−0.3) ppFEV$_1$ per year before ETI treatment, which changed to a positive slope of 3.6 (2.1–5.2) ppFEV$_1$ per year the following year. People with CF with severe lung disease at ETI initiation had one of the steepest declines in ppFEV$_1$ pre-treatment with a negative slope of −3.6 (−5.9 – −1.3) per year, and also one of the steepest increases during treatment with a positive slope of 5.1 (2.4–7.9) per year. Overall, the differences between slopes in pre-treatment and treatment periods indicated improvement in the annual rates of change of ppFEV$_1$ in all subgroups.

TABLE 1 Demographic and clinical characteristics of people with cystic fibrosis (CF) at initiation of elexacaftor/tezacaftor/ivacaftor (ETI)

	All	CFTRm pre-treated[#]	CFTRm-naïve
People with CF	392	272	120
Age years	23.0 (14.0–32.5)	22.0 (13.0–32.0)	26.0 (16.0–36.0)
Birth cohort			
1950–1979	55 (14.0)	38 (14.0)	17 (14.2)
1980–1989	68 (17.3)	41 (15.1)	27 (22.5)
1990–1999	107 (27.3)	68 (25.0)	39 (32.5)
2000–2009	97 (24.7)	74 (27.2)	23 (19.1)
2010–2016	65 (16.7)	51 (18.7)	14 (11.7)
Sex			
Male	198 (50.5)	138 (50.7)	60 (50.0)
Female	194 (49.5)	134 (49.3)	60 (50.0)
BMI z-score (age <18 years), n=139	−0.25±1.02	−0.24±0.99	−0.30±1.13
BMI kg·m^{-2} (age ⩾18 years), n=253	22.5±3.8	22.4±3.5	22.8±4.2
CF genotype			
F508del homozygous	285 (72.7)	260 (95.8)	25 (20.8)
F508del heterozygous	107 (27.3)	12 (4.4)	95 (79.2)
Sweat chloride concentration mmol·L^{-1}[¶]	94 (19)	91 (17)	99 (21)
Severity of lung disease			
Severe, ppFEV$_1$ <40	38 (9.7)	28 (10.3)	10 (8.3)
Moderate, ppFEV$_1$ ⩾40 to <70	100 (25.5)	68 (25.0)	32 (26.7)
Mild, ppFEV$_1$ ⩾70 to <90	113 (28.8)	74 (27.2)	39 (32.5)
Normal, ppFEV$_1$ ⩾90	141 (36.0)	102 (37.5)	39 (32.5)
CF-related comorbidities			
CF-related diabetes	89 (22.7)	64 (23.5)	25 (20.8)
Pancreatic insufficiency[+]	212 (93.8)	147 (93.0)	65 (95.6)
Chronic lung infection[§]	241 (61.5)	172 (63.2)	69 (57.5)

Data are presented as n, median (interquartile range), n (%) or mean±SD. CFTRm: cystic fibrosis transmembrane conductance regulator modulator; BMI: body mass index; ppFEV$_1$: percent predicted forced expiratory volume in 1 s. [#]: CFTRm therapy taken most recently prior to initiation of ETI combination includes tezacaftor/ivacaftor (n=174), lumacaftor/ivacaftor (n=93) and ivacaftor monotherapy (n=5); [¶]: data available for n=229; [+]: defined as faecal elastase-1 <200 μg·g^{-1}; data available for n=226; [§]: defined as >50% of samples positive during past 12 months for *Pseudomonas aeruginosa*, *Burkholderia cepacia* complex, *Achromobacter xylosoxidans*, *Stenotrophomonas maltophilia* and/or *Mycobacterium* species.

Change in level and slopes of ppFVC and ppFEF$_{25–75\%}$

Improvements of the lung function parameters ppFVC and ppFEF$_{25–75\%}$ were also seen. Overall, the level of ppFVC increased by 8.0 (7.1–8.9) and ppFEF$_{25–75\%}$ by 19.5 (17.0–21.9) after 12 months of ETI treatment (table 4). Levels increased among both children and adults with CF and large increases were especially seen among those without prior modulator treatment. The annual rates of change in these parameters also increased and showed continued improvement during the first year of treatment (table 5). Among all people with CF, the ppFVC slope increased from −0.4 (−1.1–0.3) to 1.7 (0.9–2.5) per year, while the ppFEF$_{25–75\%}$ slope increased from −1.7 (−3.0–−0.4) to 3.8 (2.4–5.3) per year. For all lung function parameters, the improvements were seen both among children and adults, and among CFTR modulator naïve and those pre-treated at ETI initiation.

Discussion

In an unselected nationwide CF cohort study of all people with CF aged ⩾6 years, prompt improvements in lung function were observed across all subgroups and the annual rates of change in lung function slopes reversed from negative to positive as a sign of continued improvement after 12 months.

ppFEV$_1$ levels and characteristics of people with CF

Improvements were notable across subgroups demonstrating a universal benefit of improving CFTR function both in those with severe lung disease and those with a lung function within the normal range before initiating ETI. The magnitude of the effect observed on lung function aligns with results from a phase III randomised clinical trials in tezacaftor/ivacaftor pre-treated individuals homozygous for F508del [8], and in people with CF without prior modulator treatment heterozygous for the F508del variant [9],

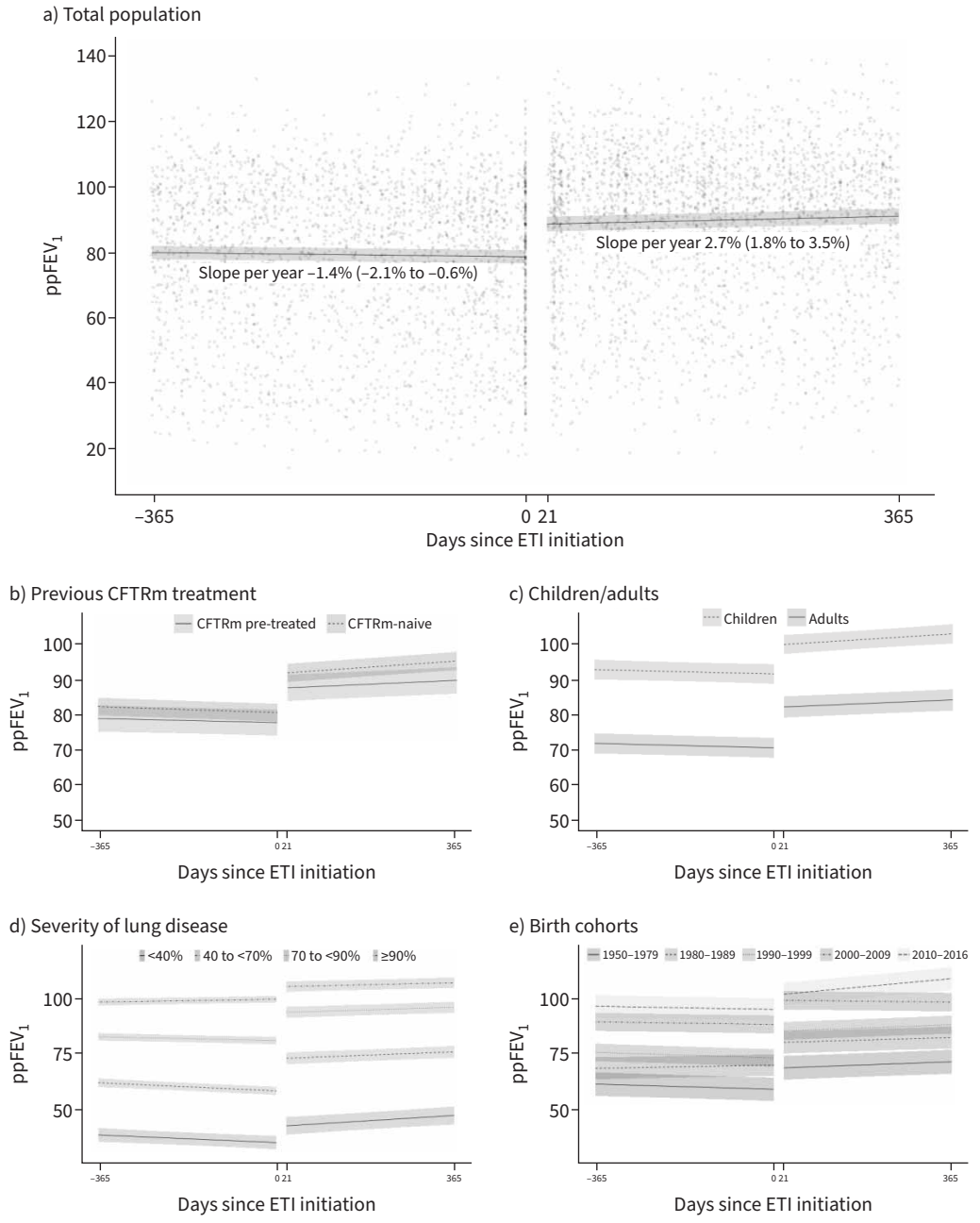

FIGURE 2 Graphs based on two-piece linear mixed models adjusted for sex and age including percent predicted forced expiratory volume in 1 s ($ppFEV_1$) measurements 12 months before and during elexacaftor/tezacaftor/ivacaftor (ETI) treatment (random effects: participant identifier and cystic fibrosis (CF) centre). a) Total population; b) previous cystic fibrosis transmembrane conductance regulator modulator (CFTRm) treatment; c) children/adults; d) severity of lung disease; e) birth cohorts. Data on lung function obtained within 21 days following ETI initiation were excluded from analysis. Estimates and slopes are presented in tables 2 and 3. Children represent people with CF aged 6–17 years at baseline. Severity of lung function is based on $ppFEV_1$ at ETI initiation.

which showed absolute changes in $ppFEV_1$ of 10.0 (7.4–12.6) and 13.8 (12.1–15.4), respectively, after 4 weeks of treatment.

Real-world studies among 9381 people with CF in the United States [20] and among 2645 people with CF in Germany [32] have reported results from annual control measurements showing increases in $ppFEV_1$ of 8.2 (8.0–8.4) and 11.3 (10.8–11.8), respectively, after 1 year of treatment. Other observational studies

TABLE 2 Percent predicted forced expiratory volume in 1 s ($ppFEV_1$) in 392 people with cystic fibrosis (CF) (4949 measurements) at initiation of elexacaftor/tezacaftor/ivacaftor (ETI) and after 12 months treatment

	Initiation of ETI	After 12 months treatment	Difference	p-value
All	78.3 (76.2–80.3)	91.2 (88.6–93.6)	13.0 (11.3–14.6)	<0.001
Previous CFTRm treatment				
CFTRm pre-treated	77.7 (75.3–80.1)	89.8 (87.2–92.4)	12.1 (10.5–13.7)	<0.001
CFTRm-naïve	79.6 (76.0–83.2)	94.1 (90.3–97.9)	15.1 (13.0–17.2)	<0.001
Severity of lung disease				
Severe, $ppFEV_1$ <40	35.1 (31.8–38.4)	47.7 (43.8–51.6)	12.6 (9.3–15.9)	<0.001
Moderate, $ppFEV_1$ ⩾40 to <70	58.9 (56.8–61.0)	76.4 (73.9–78.8)	17.4 (15.2–19.7)	<0.001
Mild, $ppFEV_1$ ⩾70 to <90	81.1 (79.1–83.1)	96.7 (94.5–98.9)	15.6 (13.5–17.8)	<0.001
Normal, $ppFEV_1$ ⩾90	99.9 (98.0–101.8)	107.9 (105.8–109.9)	8.0 (5.9–10.0)	<0.001
Child/adult at ETI initiation[#]				
Children (<18 years)	91.1 (85.5–93.8)	102.6 (100.0–105.2)	11.4 (9.8–13.1)	<0.001
Adults (⩾18 years)	69.5 (66.8–72.2)	83.4 (80.5–86.2)	13.9 (12.4–15.3)	<0.001
Birth cohorts[#]				
1950–1979	56.0 (50.6–61.3)	69.4 (63.9–74.9)	13.4 (10.6–16.3)	<0.001
1980–1989	69.3 (64.5–74.1)	82.0 (77.1–87.0)	12.7 (10.2–15.3)	<0.001
1990–1999	72.7 (68.8–76.5)	87.8 (83.8–91.8)	15.1 (13.0–17.3)	<0.001
2000–2009	87.7 (83.7–91.7)	97.9 (93.7–102.1)	10.2 (8.0–12.3)	<0.001
2010–2016	94.7 (89.8–99.6)	108.7 (103.6–113.8)	14.0 (11.4–16.6)	<0.001

Data are presented as mean (95% CI), unless otherwise stated. Estimates are based on a two-piece linear mixed model adjusted for sex and age (random effects: participant identifier and CF centre). Data on lung function obtained within 21 days following ETI initiation were excluded from analysis. CFTRm: cystic fibrosis transmembrane conductance regulator modulator. [#]: not adjusted for age.

based on spirometry data collected in clinical practice for people with CF aged ⩾12 years from France, the United States, Ireland, Italy and the Netherlands have reported changes in lung function up to 6 months after ETI initiation [15–19]. These studies found increases in $ppFEV_1$ ranging from 7.9 to 15.1. Similarly,

TABLE 3 Rate of change in percent predicted forced expiratory volume in 1 s ($ppFEV_1$ slope) in 392 people with cystic fibrosis (CF) (4949 measurements) 12 months before and 12 months after initiation of elexacaftor/tezacaftor/ivacaftor (ETI)

	Pre-treatment period	Treatment period	Difference	p-value
All	−1.4 (−2.1 – −0.6)	2.7 (1.8–3.5)	4.0 (2.9–5.2)	<0.001
Previous CFTRm treatment				
CFTRm pre-treated	−1.2 (−2.1 – −0.3)	2.3 (1.3–3.3)	3.5 (2.1–4.8)	<0.001
CFTRm-naïve	−1.8 (−3.2 – −0.3)	3.6 (2.1–5.2)	5.4 (3.3–7.5)	<0.001
Severity of lung disease				
Severe, $ppFEV_1$ <40	−3.6 (−5.9 – −1.3)	5.1 (2.4–7.9)	8.7 (5.1–12.3)	<0.001
Moderate, $ppFEV_1$ ⩾40 to <70	−3.7 (−5.3 – −2.2)	2.7 (−1.0–4.4)	6.5 (4.2–8.8)	<0.001
Mild, $ppFEV_1$ ⩾70 to <90	−1.8 (−3.1 – −0.4)	2.7 (1.2–4.2)	5.5 (2.5–6.5)	<0.001
Normal, $ppFEV_1$ ⩾90	1.3 (0.1–2.5)	2.0 (0.5–3.4)	0.7 (−1.2–5.6)	0.49
Child/adult at ETI initiation[#]				
Children (<18 years)	−1.2 (−2.5–0.01)	3.4 (1.8–4.9)	4.6 (2.6–6.6)	<0.001
Adults (⩾18 years)	−1.5 (−2.4 – −0.5)	2.1 (1.1–3.2)	3.6 (2.2–5.0)	<0.001
Birth cohorts[#]				
1950–1979	−2.5 (−4.7 – −0.4)	3.0 (0.7–5.3)	5.6 (2.4–8.7)	<0.001
1980–1989	1.4 (−0.5–3.5)	2.4 (0.4–4.4)	0.9 (−1.8–3.7)	0.51
1990–1999	−2.5 (−3.8 – −1.0)	3.0 (1.4–4.7)	5.5 (3.3–7.8)	<0.001
2000–2009	−1.2 (−2.5–0.2)	−0.9 (−2.5–0.8)	0.3 (−1.8–2.5)	0.77
2010–2016	−1.5 (−3.3–0.3)	7.5 (5.4–9.6)	8.9 (6.2–11.7)	<0.001

Data are presented as mean (95% CI), unless otherwise stated. Estimates are based on a two-piece linear mixed model adjusted for sex and age (random effects: participant identifier and CF centre). Data on lung function obtained within 21 days following ETI initiation were excluded from analysis. CFTRm: cystic fibrosis transmembrane conductance regulator modulator. [#]: not adjusted for age.

TABLE 4 Percent predicted forced vital capacity (ppFVC) and forced expiratory flow at 25–75% of FVC ($ppFEF_{25–75\%}$) in 392 people with cystic fibrosis (CF) (4949 measurements) at initiation of elexacaftor/tezacaftor/ivacaftor (ETI) and after 12 months treatment

	Initiation of ETI	After 12 months treatment	Difference	p-value
ppFVC				
All	91.7 (90.0–93.4)	99.7 (98.0–101.1)	8.0 (7.1–8.9)	<0.001
Previous CFTRm treatment				
CFTRm pre-treated	91.4 (89.3–93.4)	98.6 (96.7–100.5)	7.2 (6.3–8.2)	<0.001
CFTRm-naïve	92.4 (89.3–95.5)	102.4 (99.5–105.3)	10.0 (8.5–11.5)	<0.001
Child/adult at ETI initiation[#]				
Children (<18 years)	97.2 (94.7–99.6)	104.8 (102.6–107.3)	7.8 (6.3–9.3)	<0.001
Adults (⩾18 years)	87.8 (85.6–90.0)	95.9 (93.8–98.0)	8.0 (7.1–9.0)	<0.001
$ppFEF_{25–75\%}$[¶]				
All	58.3 (55.5–61.2)	77.8 (73.7–81.9)	19.5 (17.0–21.9)	<0.001
Previous CFTRm treatment				
CFTRm pre-treated	58.1 (54.7–61.4)	76.2 (71.9–80.5)	18.1 (15.6–20.6)	<0.001
CFTRm-naïve	59.0 (54.1–64.0)	81.9 (75.7–88.0)	22.8 (19.4–26.3)	<0.001
Child/adult at ETI initiation[#]				
Children (<18 years)	79.3 (74.6–83.9)	96.6 (90.9–102.4)	17.4 (13.9–20.9)	<0.001
Adults (⩾18 years)	44.4 (41.0–47.8)	65.2 (60.8–69.6)	20.8 (18.5–23.1)	<0.001

Data are presented as mean (95% CI), unless otherwise stated. Estimates are based on a two-piece linear mixed model adjusted for sex and age (random effects: participant identifier and CF centre). Data on lung function obtained within 21 days following ETI initiation were excluded from analysis. CFTRm: cystic fibrosis transmembrane conductance regulator modulator. [#]: not adjusted for age; [¶]: analysis on $ppFEF_{25–75\%}$ included 4922 spirometry measurements.

a United States study including an unselected population of 487 people with CF aged ⩾12 years found $ppFEV_1$ improvement of 10.3 and 9.8 at 3- and 6-month follow-up visits, respectively, after ETI initiation [19]. A single study from Italy reported on 24 months' follow-up from introduction of ETI for 36 people with CF with severe lung disease at initiation [33]. They presented 12.5 and 13.0 $ppFEV_1$ improvements

TABLE 5 Rate of change in percent predicted forced vital capacity (ppFVC) and forced expiratory flow at 25–75% of FVC ($ppFEF_{25–75\%}$) in 392 people with cystic fibrosis (CF) (4949 measurements) 12 months before and 12 months after initiation of elexacaftor/tezacaftor/ivacaftor (ETI)

	Pre-treatment period	Treatment period	Difference	p-value
ppFVC slope				
All	−0.4 (−1.1–0.3)	1.7 (0.9–2.5)	2.1 (1.1–3.1)	0.01
Previous CFTRm treatment				
CFTRm pre-treated	−0.5 (−1.3–0.3)	1.5 (0.5–2.4)	1.9 (0.7–3.2)	0.002
CFTRm-naïve	−0.3 (−1.6–1.1)	2.3 (0.8–3.7)	2.6 (0.6–4.5)	0.011
Child/adult at ETI initiation[#]				
Children (<18 years)	−0.9 (−2.4–0.6)	3.8 (2.1–5.6)	4.7 (2.3–7.2)	<0.001
Adults (⩾18 years)	−0.1 (−0.8–0.9)	0.2 (−0.7–1.2)	0.2 (−1.0–1.5)	0.79
$ppFEF_{25–75\%}$ slope[¶]				
All	−1.7 (−3.0– −0.4)	3.8 (2.4–5.3)	5.6 (3.6–7.5)	<0.001
Previous CFTRm treatment				
CFTR pre-treated	−1.5 (−3.0–0.0)	3.1 (1.3–4.8)	4.6 (2.3–6.9)	<0.001
CFTR-naïve	−2.2 (−4.7–0.3)	5.7 (3.0–8.4)	8.0 (4.4–11.6)	<0.001
Child/adult at ETI initiation[#]				
Children (<18 years)	−1.0 (−3.3–1.2)	1.3 (−1.4–4.0)	2.3 (−1.2–5.9)	0.19
Adults (⩾18 years)	−2.1 (−3.7– −0.6)	5.2 (3.6–6.9)	7.4 (5.2–9.6)	<0.001

Data are presented as mean (95% CI), unless otherwise stated. Estimates are based on a two-piece linear mixed model adjusted for sex and age (random effects: participant identifier and CF centre). Data on lung function obtained within 21 days following ETI initiation were excluded from analysis. CFTRm: cystic fibrosis transmembrane conductance regulator modulator. [#]: not adjusted for age; [¶]: analysis on $ppFEF_{25–75\%}$ included 4922 spirometry measurements.

after the first and second year, respectively. Our study confirms these findings and adds to the limited data among people with CF aged 6–11 years.

We observed that improvement in lung function was not constrained by initial lung disease severity, confirming previous similar findings [18, 32]. The large benefits of ETI among people with CF with mild and moderate lung disease highlights the potential for good outcomes in those with less irreversible tissue damage, and room for improvement before reaching their physiological ceiling for lung function.

Annual rate of change in ppFEV$_1$

By assessing the annual rates of change in spirometry parameters, this study shows that improvements in lung function were sustained during the first 12 months of ETI treatment. These findings underscore that ETI not only halts the progressive loss of lung function that has been a hallmark of CF disease, but also leads to a continuing improvement in all spirometry outcomes over the first year, especially among people with CF with severe lung disease at treatment initiation. A previous study used annual lung function data to estimate the rate of change and found a slope of 0.39 (−0.06–0.85) ppFEV$_1$ per year during the first 2 years of ETI treatment [22]. This was a follow-up study among participants of a clinical trial representing a pre-selected population. The present study included a clinically unselected population, and yet a 4% improvement of slopes was seen overall compared to the year before ETI. This robust estimation provides a promising outlook for people with CF, which will likely be reflected in delayed onset of CF-associated lung complications, reduced need for lung transplantation and increased life expectancy [34].

Effects on additional indicators of lung function

The largest improvement in a lung function parameter was seen in ppFEF$_{25–75\%}$, with a change of 19.5 (17.0–21.9) indicating a substantial drop in peripheral airway obstruction. This confirms that FEF$_{25–75\%}$ is a sensitive indicator of airflow as seen in the initial stages of small airway disease in both children and adults with CF [35]. One other study has reported an increase of of 7.0 in ppFEF$_{25–75\%}$ following ETI [18].

We observed that ppFVC increased by 8.0 (7.1–8.9), indicating larger total lung volume as a sign of greater accessibility to the more peripheral parts of the lungs, possibly due to better mucus clearance [36]. Three studies have reported increases in ppFVC between 6.9 and 13.3 [16, 19, 37]. The available evidence suggests that the CF-specific vicious cycle of airway obstruction, infection and inflammation has been broken by the introduction of ETI, at least temporarily. This is supported by evidence of reduced infection rates and antibiotic usage after introduction of ETI [38]. The observed effects raise the question of which parameters will be most suited to monitoring of lung disease progression in CF in the future. ppFEF$_{25–75\%}$, gas-trapping on high-resolution computed tomography and Lung Clearance Index may all be important measures in assessment of early-stage lung disease, especially in settings where multiple-breath washout is not accessible [39].

Strengths and limitations

The data included in this study are from an unselected nationwide cohort, including all individuals who initiated ETI treatment in Denmark during the study period. In addition, people with CF were monitored closely, with physical consultations and spirometry every 1–2 months, which is the Danish standard of care for CF [25]. This provided a high resolution of data allowing for robust prediction of annual rates of change in lung function. The majority of people with CF aged ⩾12 years initiated ETI in Denmark between September 2020 and June 2021, coinciding with the coronavirus disease 2019 (COVID-19) pandemic. Despite fewer visits to the Danish CF centres, the resolution in lung function data was still very high, with a median of 12 spirometry measurements per person, evenly distributed between the before and after periods. The pre-treatment period is more likely to have been affected by COVID-19 risk reduction measures, which may have led to better lung function and thus underestimated the impact of ETI. Nevertheless, all real-world studies of ETI have been implemented during the COVID-19 pandemic, and their results are still in line with the clinical pre-pandemic trials, indicating that the pandemic had little influence on the observed data. Finally, our study did not include information about change in use of other medication, diet or physical exercise, nor how nonmodulator-related factors could have contributed to the improved lung function.

Conclusion

Danish people with CF across age groups, disease severities and prior modulator treatment improved their lung function as measured by ppFEV$_1$, ppFVC and ppFEF$_{25–75\%}$ 1 year after initiation of ETI. The annual rates of change in lung function improved from negative to positive slopes, marking a halt in lung disease progression during the first year of treatment. Longer-term studies will be essential for following these trends and assessing the impact of CFTR modulator therapy on CF lung disease.

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