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Original Article

Determinants of early Elexacaftor-Tezacaftor-Ivacaftor use in adults with cystic fibrosis and preserved lung function: insights from a European multicenter survey

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ABSTRACT

Background: Limited evidence exists to guide Elexacaftor-Tezacaftor-Ivacaftor (ETI) use in adults with cystic fibrosis (awCF) and preserved lung function (ppFEV1 >90%). To address the resulting variability in prescribing practices, we conducted a European survey among a group of adult CF centres aiming at identifying factors influencing ETI initiation decisions in adults with preserved lung function.

Methods: Between April and June 2024, we invited 25 ECFS prescribers from 25 adult CF centres to participate in a web-based survey to explore factors influencing ETI initiation in adults with CF and $ppFEV_1$ >90%. The survey questionnaire collected data on centre characteristics, prescribing ETI attitudes, and the impact of specific clinical variables on ETI prescription decision in this subgroup.

Results: Twenty-three CF specialists (92%) responded. Most specialists (69.6%) favoured early treatment initiation in all eligible patients. A key factors influencing ETI initiation decisions was the presence of respiratory symptoms. In adults with preserved lung function, however, microbiological and imaging features emerged as the most influential factors driving treatment decision. While patient willingness and symptoms strongly encouraged ETI use, factors like age over 50, a history of mental health issues, and pregnancy desire resulted in conflicting prescribing attitudes among centers.

Conclusions: Although several disease markers more consistently support the decision to initiate ETI in individuals with preserved lung function, the absence of clear clinical guidance contributes to heterogeneous prescribing practices across centres. This highlights the need for longitudinal studies to clarify the long-term outcomes of ETI in this population.

1. Introduction

Cystic fibrosis transmembrane conductance regulator (CFTR) modulators have transformed the treatment landscape for individuals with cystic fibrosis (CF). The introduction of Elexacaftor/Tezacaftor/Ivacaftor (ETI) has led to significant improvements in lung function, body mass index (BMI), frequency of pulmonary exacerbations and respiratory symptoms in eligible individuals [1–3]. Real-world studies have corroborated these benefits, even among individuals with advanced CF lung disease, a population initially excluded from clinical trials, demonstrating a substantial reduction in lung transplantation rates [4, 5].

To date, there is limited evidence to guide the use of ETI in adults with cystic fibrosis (awCF) who have a percent predicted FEV_1 ($ppFEV_1$) greater than 90%, since this represents the upper threshold for inclusion in CFTR modulator clinical trials. A recent analysis of prescribing patterns in the United States found that most of the individuals in this subgroup were not prescribed ETI, reflecting a more conservative approach and highlighting the ongoing uncertainty around treatment decisions in those with preserved lung function [6]. Neither clinical trials nor current guidelines offer specific recommendations for this patient group, leaving treatment decisions to the discretion of individual CF centres and patient preferences. This lack of standardised guidance may lead to considerable variability in care, not only between countries but also among centres within the same country. This highlights the need to better understand current prescribing practices and their underlying rationale.

To address this, we conducted a survey across 25 European CF centres to identify the factors influencing the decision to initiate ETI in awCF and preserved lung function.

2. Methods

We developed a web-based survey using the SurveyMonkey platform. The questionnaire covered demographic, diagnostic, clinical, radiologic, and microbiologic domains, with the aim of identifying factors considered most relevant when deciding whether to initiate ETI in adults with awCF with preserved lung function. Preserved lung function was pragmatically defined as $ppFEV_1$ >90%, reflecting the threshold above which individuals were typically excluded from CFTR modulator trials.

The survey was electronically distributed to CF specialists across Europe between April and June 2024. Participation was voluntary and anonymous. To minimise selection bias and promote broad representation, invitations were sent to European Cystic Fibrosis Society (ECFS)-affiliated CF stakeholders across diverse geographic regions and centre profiles. Responses were obtained from centres in 15 countries. Participants were instructed to complete the survey based on their centre's experience and local prescribing practices, referring to routine clinical practice rather than individual preferences. In cases where approaches varied among clinicians within the same centre, respondents were asked to report the strategy most reflective of the prevailing standard practice or general orientation of their institution. Centres caring for both paediatric and adult patients were specifically asked to provide responses pertaining to adult clinical practice only.

Survey data were organised into three main sections for analysis. The first section collected information on centre and respondent characteristics, including years of experience, centre size and geographical location. The second section comprised five general statements to assess each centre's overall attitude towards prescribing ETI in eligible individuals. Respondents indicated their level of agreement with each statement using a five-point Likert scale ranging from "*Strongly disagree*" to "*Strongly agree*." In the third section, respondents rated the influence of specific individual variables on their decision to initiate ETI in individuals with preserved lung function, using a five-point scale where 1 indicated "s*trongly dissuades me from proposing ETI*", 2 "dissuades me to propose ETI", 3 "nor dissuades nor leads me to propose ETI", 4 "leads me to propose ETI", and 5 "s*trongly leads me to propose ETI*".

All responses were analysed descriptively. Categorical variables were presented as frequencies and percentages. Heatmaps were used as a

visual aid to enhance interpretation of responses to scale-based questions.

3. Results

From April to June 2024, 25 CF physicians caring for awCF and active ECFS members were invited to participate in the survey, with 23 centres ultimately contributing to the project. Respondent and centre characteristics are summarised in Table 1. The geographical distribution of the centres was 34% from Southern Europe, 22% each from Western, Eastern, and Northern Europe (Fig. 1).

When inquiring the general attitude towards ETI prescription, the majority of centres (74%) were inclined to offer ETI to eligible awCF and initiate therapy as soon as possible (Table 2). However, more than a half of respondents (57%) agreed that the decision to initiate treatment was influenced by individual clinical characteristics, particularly respiratory symptoms (61%) and nutritional status (57%). However, this perspective was not uniform across centres, as approximately one third of respondents disagreed that such individual factors should influence the timing of ETI initiation.

Fig. 2 summarizes the responses related to specific factors influencing the decision to initiate treatment in awCF and preserved lung function, including demographics, diagnostics, radiological, clinical and microbiological variables.

Demographics. Among demographic factors, age and sex did not appear to significantly influence the decision to initiate ETI. However, physicians were more hesitant to suggest ETI in individuals over 50 years of age, with 22% indicating greater caution in this subgroup.

Diagnosis. A total of 65% of respondents would refrain from prescribing ETI in the context of a CFTR-related disorder (CFTR-RD) diagnosis, whereas intermediate sweat chloride values had minimal influence on prescribing decisions for most participants. The likelihood of initiating ETI in individuals with at least one *F508del* variant varied depending on the second allele. The presence of an FDA-approved variant on the second allele either encouraged (44%) or strongly encouraged (35%) physicians to initiate treatment. When 5T-12TG was present, 48% of respondents were inclined to prescribe ETI. Similarly, other less well-characterized variants with variable clinical consequences elicited mixed responses, reflecting ongoing uncertainty and variability in their clinical interpretation.

Microbiology. Respiratory microbiology emerged as one of the most influential factors driving ETI initiation in awCF and preserved lung function. Prior detection of *Pseudomonas aeruginosa* had a strong impact, with 78% of respondents indicating that it either encouraged (30%) or strongly encouraged (48%) the decision to initiate treatment. Other indicators of chronic airway infection, positive sputum cultures, previous detection of non-tuberculous mycobacteria (NTM) and at least one antibiotic course in the previous year, also supported ETI initiation in 78%, 74%, and 74% of respondents, respectively.

Radiological findings. Radiological status was another key factor influencing the decision to start ETI. The presence of any CF-related abnormality on chest CT was more persuasive than abnormalities on chest radiograph, prompting treatment in 87% versus 78% of respondents. Among specific CT findings, bronchial wall thickening, bronchiectasis, and mucus plugging were the most influential, guiding the decision to initiate ETI in 83%, 83%, and 78% of respondents, respectively. In contrast, air trapping was considered less relevant, with 61% of respondents indicating it impacted their decision.

Comorbidities. CF-related comorbidities and concomitant conditions had a variable impact on the decision to initiate ETI. Common CF-related comorbidities, such as chronic sinusitis (78%) and CF-related diabetes (CFRD) (78%), were perceived as important drivers supporting ETI initiation. Most respondents (83%) reported being more inclined to prescribe ETI in underweight patients, whereas only a minority (30%) were dissuaded by the presence of overweight or obesity. A history of mental health conditions appeared to negatively influence prescribing decisions, with 39% of respondents reporting it as discouraging and 4% as strongly discouraging.

Treatment-related factors. Ongoing therapies also influenced the decision to initiate ETI. The prescription of airway clearance techniques and inhaled mucoactive therapies encouraged treatment initiation in 52% and 61% of respondents, respectively. Previous use of other CFTR modulators yielded more heterogeneous responses: while 78% were encouraged to prescribe ETI when a clinical benefit had been observed, opinions were more divided when no improvement was reported.

Patient-related factors. Several patient-related factors, particularly symptoms and treatment preferences, played a significant role in decision-making. Patient willingness to start therapy, along with the presence of chronic cough and sputum production, were each associated with a strong preference to initiate ETI, as reported by 87% of respondents. Desire for pregnancy was also a factor. While 35% of respondents reported being discouraged or strongly discouraged from prescribing ETI in this context, an equal proportion (35%) was positively influenced.

Table 1
Characteristics of the respondents and their centres.

Characteristic	$N = 23$[1]
Male sex	10/23 (43.5%)
Specialty	
Pulmonology	19/23 (82.6%)
Pediatrics	3/23 (13.0%)
Geriatrics	1/23 (4.3%)
Years qualified	
>20	15/23 (65.2%)
11–20	4/23 (17.4%)
5–10	4/23 (17.4%)
<5	0/23 (0.0%)
Years involved in CF	
>20	10/23 (43.5%)
11–20	5/23 (21.7%)
5–10	7/23 (30.4%)
<5	1/23 (4.3%)
Geographical area	
Northern Europe	5/23 (21.7%)
Western Europe	5/23 (21.7%)
Southern Europe	9/23 (39.1%)
Eastern Europe	4/23 (17.5%)
Number of patients followed by the Centre	
≥200	15/23 (65.2%)
<200	8/23 (34.8%)
Centre population	
Adults	15/23 (65.2%)
Mixed adults and children	8/23 (34.8%)
Centres with eligible awCF with ppFEV1 >90 but not taking ETI?	20/23 (87.0%)
Percentage of eligible awCF with ppFEV1 >90 currently not treated	
Median (Q1; Q3)	12.5 (5.0(2%); 22.5 (50%))
Was this decision:	
Agreed upon within the multidisciplinary team	14/19 (73.7%)
Made by the individual physician	5/19 (26.3%)
Whose decision was?	
Shared decision	16/20 (80.0%)
Patient's	4/20 (20.0%)
Physician's	0/20

[1]n/N (%)

Acronym. CF: cystic fibrosis; awCF: adults with CF; ETI: Elexacaftor/Tezacaftor/Ivacaftor.

4. Discussion

This study explored the factors influencing the initiation of ETI therapy in awCF with preserved lung function. In the absence of evidence-based data and formal recommendations for this specific population, treatment decisions are largely guided by expert opinion and the clinical judgment of individual centres. While most respondents

Fig. 1. Geographical distribution of the participating centres.

Table 2
Centres attitude towards ETI prescription.

I start ETI …	Strongly disagree	Disagree	Neither agree nor disagree	In agreement	Strongly agree
In all eligible patients (according to each country's legislation)	4.3	17.4	8.7	34.8	34.8
As soon as possible	0	8.7	17.4	34.8	39.1
Based on individual characteristics	8.7	30.4	4.4	21.7	34.8
Mainly due to respiratory symptoms	4.4	26.1	8.7	21.7	39.1
Mainly due to nutritional concerns	4.4	26.1	13.0	26.1	30.4

Data represent the percentage of responses provided by the 23 CF specialists surveyed.

supported early initiation of ETI in all individuals with eligible *CFTR* genotypes in general, a more personalised approach was favoured in this population, with individual characteristics playing a significant role in guiding prescribing decisions. This survey provides novel insights into how CF specialists assess and prioritise clinical, diagnostic, and patient-related factors, in real-world practice.

Demographic factors such as age and sex did not appear to significantly influence the decision to initiate ETI in most cases. However, age over 50 years was considered a discouraging factor by some respondents. This likely reflects an implicit clinical reasoning: since CF lung disease typically develops early in life, reaching older age without marked respiratory involvement may be interpreted as evidence of a milder disease trajectory and lower risk of future decline [7]. As ETI is often prescribed with the aim of preventing long-term progression, clinicians may exercise more caution when initiating treatment in older individuals who appear to have remained relatively stable over time.

Although sex was not considered a major factor by most respondents, a notable minority reported that female sex encouraged ETI prescription. This finding aligns with existing literature on sex-based disparities in CF outcomes, where females are known to experience faster lung function decline and poorer overall prognosis [8]. This tendency is further supported by data from the 2024 UK CF Registry, which showed that this gender gap appears to be closing, an effect that may be attributable to the widespread use of CFTR modulators [9].

Genotype remains a key factor in ETI prescribing, as regulatory approvals are still primarily based on the presence of at least one responsive CFTR variant. Our results further expand on a previous structured interview study, which found that decisions to prescribe CFTR modulator therapies were primarily based on genotype rather than disease severity [10]. In this context, we examined whether the nature of the second CFTR variant influenced prescribing behaviour. When the second variant was listed among FDA-approved variants for ETI, most clinicians reported a clear inclination to initiate treatment [11]. It should be noted that these responses were collected before the recent EMA recommendation to expand ETI use to patients aged ≥2 years with at least one non–Class I CFTR mutation [12]. The presence of 5T-12TG, typically associated with a milder phenotype and reduced incidence of CF-related complications [13], led to more variable responses, although the majority of clinicians still leaned toward prescribing ETI. This reflects the ongoing uncertainty surrounding the long-term clinical implications of this genotype. Nonetheless, most respondents indicated that the functional role of the second mutation did not strongly influence their decision.

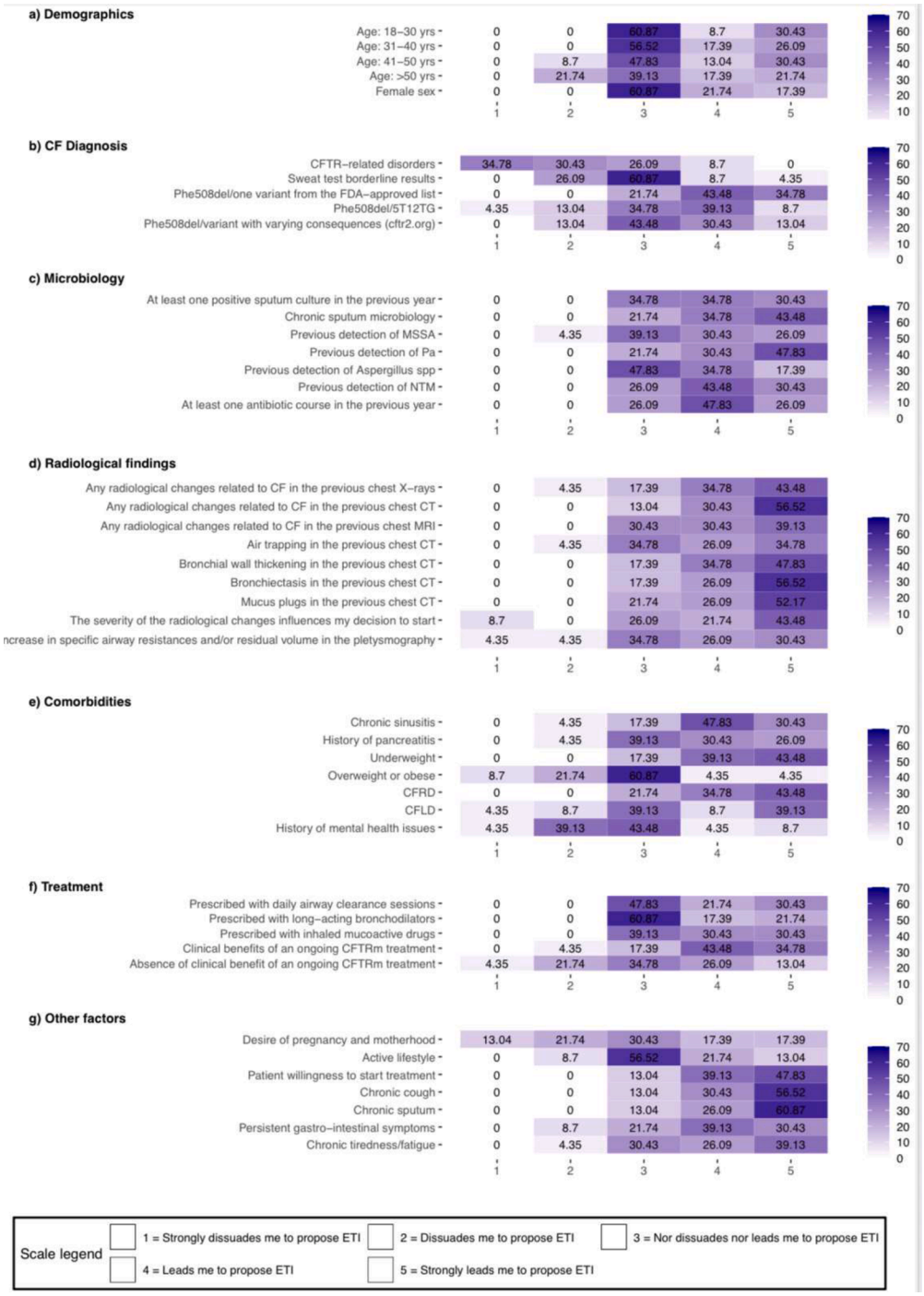

Fig. 2. Heatmap of the factors influencing ETI prescription in pwCF with preserved lung function.
Responses were given on a five-point scale, where 1 indicated "Strongly dissuades from proposing ETI", 2 "dissuades me to propose ETI", 3 "nor dissuades nor leads me to propose ETI", 4 "leads me to propose ETI", and 5 "Strongly leads to propose ETI".

A diagnosis of CFTR-RD was generally perceived as a discouraging factor for prescribing ETI, given that CFTR modulators are not approved or reimbursed for this indication [14]. Nevertheless, the willingness of a minority of respondents to consider ETI in this group reflects the view that, when CFTR dysfunction results in measurable clinical impact, some individuals might still derive clinical benefit. Overall, these findings suggest that while CFTR genotype remains a key determinant, clinical and contextual factors are also carefully weighed when evaluating ETI initiation in adults with CF who have preserved lung function.

Traditional microbiological markers played a central role in guiding treatment decisions. Among these, prior detection of *P. aeruginosa* emerged as one of the most influential factors, prompting ETI initiation in nearly 80% of respondents. This aligns with previous findings by Hergenroeder et al. [6] and reflects the well-established association between *P. aeruginosa* infection, poorer clinical outcomes in CF and early therapeutic intervention [15–17]. Within this context, ETI may be viewed as a potentially beneficial strategy.

Other microbiological indicators, such as chronic sputum infection, prior detection of NTM, and recent need for antibiotic treatment (which was a proxy for exacerbations), were also perceived as signs of underlying disease activity, and thus supported the decision to start ETI [17–19]. In contrast, the presence of *Aspergillus* spp. had a more limited

impact on prescribing decisions. This likely reflects the less defined role of fungi in disease progression, along with the limited evidence of clinical benefits related to *Aspergillus* reduction following ETI therapy [20]. In addition, our results align with a previous study based in the United States reporting that the presence of methicillin-resistant *Staphylococcus aureus* (MRSA) was associated with higher ETI prescription rates [6], likely due to its known association with worse clinical outcomes [21].

Chest CT findings, especially those revealing structural lung changes, were among the most influential factors guiding clinicians towards ETI initiation. The presence of bronchiectasis, bronchial wall thickening and mucus plugging emerged as strong indicators for starting treatment. In contrast, air trapping generated more variable responses among clinicians. A study by Brody et al. examining chest CT scans in 60 individuals with mild to moderate CF lung disease reported air trapping in 63% of cases. However, this feature is often under-recognized, as detection typically requires paired inspiratory and expiratory imaging, an approach that is not routinely used in clinical practice due to concerns about cumulative radiation exposure [22–23]. Nonetheless, a correlation has been observed between radiological air trapping and hyperinflation measured through pulmonary function tests [22]. Notably, hyperinflation itself has been associated with reduced FEV1 increase after CFTR modulators in individuals with advanced lung disease, underscoring the relevance of early detection [23]. In this context, body plethysmography may serve as a valuable tool for assessing air trapping in patients with preserved lung function. This is further supported by our survey findings, where more than half of respondents indicated that elevated airway resistance or increased residual volume were factors encouraging ETI initiation. These responses suggest that CF physicians may view early therapeutic intervention, in the presence of initial physiological abnormalities, as a strategy to potentially slow disease progression.

As expected, CF-related complications, such as chronic sinusitis, CFRD, malnutrition and a history of pancreatitis, were generally associated with a higher likelihood of ETI prescription. In contrast, the presence of overweight or obesity discouraged nearly one-third of respondents from initiating treatment. Previous studies have shown that weight gain following ETI initiation is variable and influenced by baseline BMI as well as the presence of residual function variants [24]. While underweight individuals often experience beneficial weight normalization, weight gain has also been reported in those with normal or elevated baseline BMI. This has raised concerns about the potential progression to overweight or obesity following ETI, highlighting the importance of close nutritional monitoring during treatment [24]. However, the limited hesitation in initiating ETI in obese adults with preserved lung function likely reflects the prevailing view of ETI as a disease-modifying therapy targeting the underlying CFTR defect, rather than a treatment driven solely by the degree of respiratory impairment.

The presence of mental health issues also emerged as a discouraging factor in ETI prescription decisions. This reflects growing evidence suggesting a potential association between ETI therapy and the emergence of exacerbation of mental health symptoms, including depression, anxiety and sleep disturbances. However, available data remain inconclusive. While some studies report improvements in mental health among younger patients, others have observed a worsening of symptoms, particularly in older individuals [25–28]. In light of these uncertainties, clinicians may perceive the risk–benefit ratio as less favourable for individuals with mild or no respiratory disease, contributing to more cautious prescribing in this subgroup.

Regarding chronic therapies, it is unsurprising that respondents were more likely to prescribe ETI to awCF using airway clearance techniques or inhaled mucoactive agents, as these treatments often reflect the presence of chronic sputum production and bronchiectasis [29–31]. In contrast, bronchodilator use had minimal influence on prescribing decisions, aligning with the limited evidence supporting their routine use in individuals with CF [32–33]. When considering previous treatment with other CFTR modulators, the decision to initiate ETI was generally based on the clinical response observed: a favourable prior response encouraged ETI prescription, whereas a lack of benefit raised hesitation, with nearly one-third of respondents discouraged from initiating ETI. This likely reflects a perception that a poor response to earlier modulators may indicate a milder disease phenotype with a reduced potential for further clinical improvement.

Patient-related factors played a central role in ETI prescribing decisions. Respiratory symptoms, particularly chronic cough and sputum production, were among the most influential clinical indicators, likely reflecting clinicians' perception of established or ongoing lung disease. Patient willingness to initiate treatment was also highly valued by most respondents, underscoring the importance of shared decision-making and active patient engagement in the management chronic conditions [34]. Notably, approximately 20% of decisions not to initiate ETI were reported to be driven solely by patient choice. These findings emphasize the need for structured and comprehensive discussions with patients and reinforce that patient preferences should be explicitly integrated into treatment decision-making, especially in the context of long-term therapies.

Responses regarding ETI prescription in women planning pregnancy were highly divided. This likely reflects the limited data on both pregnancy outcomes in women with CF and the safety of CFTR modulators during pregnancy and lactation [35]. The focus on individuals with preserved lung function may explain the divergence: some clinicians may feel the modest expected benefit of ETI does not outweigh potential risks, while others see ETI as a protective measure against the physiological demands of pregnancy in CF [36]. As health outcomes continue to improve and CFTR modulators become standard, this issue will grow in importance, highlighting the urgent need for clearer, evidence-based guidance.

Although respondents encompassed a range of European countries and included physicians with varying levels of experience from centres of different sizes, we acknowledge that the voluntary nature of participation may have introduced a selection bias. Furthermore, as the survey relies primarily on a single-expert responses per centre, the collected opinions may not fully reflect actual prescribing behaviour in routine clinical practice.

Despite efforts were made to ensure broad geographic representation, the relatively small number of participating centres may limit the generalisability of the findings, given the substantial variability across regions in access to and reimbursement for CFTR modulators, as well as in local treatment practices [37]. In addition, as this study reflects prescribing practices within European healthcare settings, the applicability of these findings to non-European regions may be limited, considering differences in healthcare systems, drug availability, reimbursement structures and prescribing paradigms worldwide.

Finally, this survey captures prescribing practices solely from the perspective of healthcare professionals. As highlighted by the findings, patient perspectives play an important role in shared decision-making and may influence prescribing behaviour. Future studies should therefore incorporate patient-reported perspectives to provide a more comprehensive understanding of treatment decisions in awCF.

5. Conclusion

Our findings reveal heterogeneity and areas of uncertainty in ETI prescribing among adults with CF and preserved lung function. Traditional markers of disease activity, such as microbiological findings and respiratory symptoms, remain key drivers of treatment initiation. However, greater caution is observed in older individuals, those with overweight/obesity, and patients with pre-existing mental health conditions, highlighting emerging concerns in the post-ETI era and the need for clearer guidance. Pregnancy remains a particularly divisive scenario, reflecting limited high-quality evidence. Overall, as CFTR modulator use expands to individuals with milder disease, more structured and

evidence-informed risk–benefit assessment will be essential.

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CRediT authorship contribution statement

Andrea Gramegna: Conceptualization, Data curation, Writing – original draft. **Carlo Magnoni:** Conceptualization, Data curation, Writing – review & editing. **Chiara Premuda:** Conceptualization, Data curation, Writing – original draft. **Gianfranco Alicandro:** Data curation, Formal analysis. **Onno Akkerman:** Data curation, Writing – review & editing. **Adelina Amorim:** Data curation, Writing – review & editing. **Pilar Azevedo:** Data curation, Writing – review & editing. **Stephen Bourke:** Data curation, Writing – review & editing. **Vincenzo Carnovale:** Data curation, Writing – review & editing. **Filia Diamantea:** Data curation, Writing – review & editing. **Libor Fila:** Data curation, Writing – review & editing. **Freddy Frost:** Data curation, Writing – review & editing. **Rosa Maria Giron Moreno:** Data curation, Writing – review & editing. **Camelia Pescaru:** Data curation, Writing – review & editing. **Eva Polverino:** Data curation, Writing – review & editing. **Almudena Felipe Montiel:** Data curation, Writing – review & editing. **Marta Rachel:** Data curation, Writing – review & editing. **Gergana Petrova Stoyanova:** Data curation, Writing – review & editing. **Eva Van Braeckel:** Data curation, Writing – review & editing. **Sonia Volpi:** Data curation, Writing – review & editing. **Andrea Vukić -Dugac:** Data curation, Writing – review & editing. **Sabine Wege:** Data curation, Writing – review & editing. **Nicholas J. Simmonds:** Data curation, Writing – review & editing. **Barry J. Plant:** Data curation, Writing – review & editing. **Damian G. Downey:** Data curation, Writing – review & editing. **Silke van Koningsbruggen-Rietschel:** Data curation, Writing – review & editing. **Pierre-Régis Burgel:** Data curation, Writing – review & editing. **Francesco Blasi:** Conceptualization, Writing – review & editing.

Declaration of competing interest

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Supplementary materials

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