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Use of elexacaftor+tezacaftor+ivacaftor in individuals with cystic fibrosis and at least one *F508del* allele: a systematic review and meta-analysis

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ABSTRACT

Objective: To evaluate the effect of treatment with the combination of three cystic fibrosis transmembrane conductance regulator (CFTR) modulators—elexacaftor+tezacaftor+ivacaftor (ETI)—on important clinical endpoints in individuals with cystic fibrosis. **Methods:** This was a systematic review and meta-analysis of randomized clinical trials that compared the use of ETI in individuals with CF and at least one *F508del* allele with that of placebo or with an active comparator such as other combinations of CFTR modulators, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations and the Patients of interest, Intervention to be studied, Comparison of interventions, and Outcome of interest (PICO) methodology. We searched the following databases: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov from their inception to December 26th, 2022. The risk of bias was assessed using the Cochrane risk-of-bias tool, and the quality of evidence was based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE). **Results:** We retrieved 54 studies in the primary search. Of these, 6 met the inclusion criteria and were analyzed (1,127 patients; 577 and 550 in the intervention and control groups, respectively). The meta-analysis revealed that the use of ETI increased FEV_1% [risk difference (RD), +10.47%; 95% CI, 6.88-14.06], reduced the number of acute pulmonary exacerbations (RD, −0.16; 95% CI, −0.28 to −0.04), and improved quality of life (RD, +14.93; 95% CI, 9.98-19.89) and BMI (RD, +1.07 kg/m^2; 95% CI, 0.90-1.25). Adverse events did not differ between groups (RD, −0.03; 95% CI, −0.08 to 0.01), and none of the studies reported deaths. **Conclusions:** Our findings demonstrate that ETI treatment substantially improves clinically significant, patient-centered outcomes.

Keywords: Cystic fibrosis/therapy; Cystic fibrosis transmembrane conductance regulator; Membrane transport modulators.

INTRODUCTION

Cystic fibrosis (CF) is a genetic disease that results in dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) protein, a chloride and bicarbonate channel expressed in the apical portion of epithelial cells of several organs of the human body.[1] CFTR protein dysfunction results in diverse and potentially severe clinical manifestations, primarily involving the respiratory, gastrointestinal, and reproductive systems, reducing quality of life and life expectancy.[2] More than 2,000 variants have been described as related to CF or CF-like manifestations, and the most common variant worldwide has at least one *F508del* allele,[3] reported in approximately 60% of CF individuals in Brazil.[4]

Described more than 70 years ago, CF is yet a condition with no definitive cure, although it has now a totally different and much more favorable therapeutic and prognostic horizon for affected individuals than in the past.[5] This new scenario of hope was created mainly by the discovery of CFTR protein modulators, small molecules that have been shown to be able to rescue protein function or expression.[6] The first CFTR modulator described, ivacaftor, interacts with mutant CFTR proteins expressed at the cell surface and increase channel activity; therefore, it has been labeled as a 'potentiator'.[7] Because F508del mutant proteins have defective processing and trafficking at the endoplasmic reticulum, the use of molecules able to increase protein expression is critical to rescue CFTR function[8]; some of these compounds, named "correctors," have also been identified (lumacaftor, tezacaftor, and elexacaftor).[9] However, F508del mutant proteins rescued by these correctors do not exhibit sufficient channel activity when expressed at the cell surface, and, therefore, there is a need to combine at least one corrector with a potentiator to promote significant CFTR function.[8]

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Initial results of combination therapies in *F508del* homozygous CF patients showed less expressive improvements in lung function compared to the effects of ivacaftor for individuals with gating variants.[6] A step forward was the recognition that F508del CFTR mutants have more than one critical defect that needs to be tackled to overcome the endoplasmic reticulum checkpoints of protein quality and to result in CFTR expression at the cell membrane.[10,11] These findings led to clinical trials testing the combination of two correctors and a potentiator (ivacaftor) to rescue F508del CFTR mutants, the combination of elexacaftor+tezacaftor+ivacaftor (ETI).[12]

Initial results of the studies of ETI use for CF individuals with F508del CFTR variants were promising, and even patients with only one copy of the variant allele combined with another minimal function variant allele showed substantial improvements in key outcomes such as lung function, quality of life, nutrition, and frequency of exacerbations.[12-14] Subsequently, initial results of pivotal studies, extension studies, and interventions in different age groups were also published.[15,16]

In Brazil, recently published clinical practice guidelines[17] focusing on the treatment of CF did not include a question regarding the use of ETI in CF patients because their clinical questions had been developed before this drug combination was available in the country. However, this reality is rapidly changing, and given that F508del CFTR mutations are the most prevalent type of mutations causing CF worldwide, it is important to estimate the cumulative effect of ETI on important clinical outcomes in patients with CF. Therefore, we conducted a systematic review and meta-analysis on the effects of ETI in patients with CF and at least one *F508del* allele.

METHODS

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[18]

The study protocol followed the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework, and the question of interest followed the Patients of interest, Intervention to be studied, Comparison of interventions, and Outcome of interest (PICO) methodology. With the use of highly effective CFTR modulators as the intervention of interest, the PICO framework was as follows: Patients, patients with CF; Intervention, use of elexacaftor+tezacaftor+ivacaftor; Comparison, other modulators or placebo; and Outcome, mortality rate due to any cause, acute pulmonary exacerbations, adverse events, lung function (measured by FEV_1), quality of life (measured by the respiratory domain score of the Cystic Fibrosis Questionnaire), and BMI.

We aimed to include all randomized controlled trials (RCTs) on the topic. No restrictions were imposed with regard to the date of publication, language, age group, or availability of full texts of papers. The protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) platform (Protocol no. 2023 CRD42023386782).

Two authors developed search strategies that were revised and approved by the team, selected information sources, and systematically searched the following databases: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov. A specific search strategy was used for the databases: (Fibrosis Cystic OR Mucoviscidosis OR Pulmonary Cystic Fibrosis OR Pancreatic Cystic Fibrosis OR Fibrocystic Disease of Pancreas OR Pancreas Fibrocystic Disease OR Pancreas Fibrocystic Diseases OR Cystic Fibrosis of Pancreas) AND (elexacaftor ivacaftor tezacaftor OR elexacaftor ivacaftor tezacaftor drug combination OR Trikafta OR VX445); For the Cochrane Central Register of Controlled Trials, the following strategy was used: fibrosis cystic AND elexacaftor ivacaftor tezacaftor.

Two researchers independently selected and extracted data from the studies included. First, studies were selected based on their titles and abstracts. Then, the full texts were evaluated for inclusion or exclusion, and disagreements were resolved by consensus or following a discussion with a third researcher. Data regarding authorship, year of publication, patient description, interventions (ETI and control), absolute numbers of each outcome, and follow-up duration were extracted from the studies by two researchers independently, and the extracted values were compared.

The risk of bias for RCTs was assessed using the modified Cochrane risk-of-bias tool (RoB 2),[19,20] as were other fundamental elements, and were expressed as very serious, serious, or non-serious. The risk of bias assessment was conducted by two reviewers independently, and, in case of disagreement, a third reviewer deliberated the assessment. The quality of the evidence was extrapolated from the risk of bias based on the GRADE terminology as very low, low, or high, using the GRADEpro Guideline Development Tool (McMaster University, Hamilton, ON, Canada).[21]

Categorical outcomes were expressed by group (ETI and control), as was the calculated risk in percentage (by dividing the number of events by the total number of patients in each group). If the risk difference (RD) between the groups was significant, a 95% CI was expressed, and the number needed to treat or the number needed to harm was calculated. Continuous outcomes were expressed by groups (ETI and control) as means and standard deviations, as well as the risk difference between the groups.

We used a fixed-effect or a random-effect model for the meta-analysis to evaluate the effect of ETI vs. control on the outcomes of interest when these data were available in at least two RCTs. The effects were reported as RDs and corresponding 95% CIs; a 95% CI which encompassed the value 0 in its range indicated that there was no difference in the effect between the ETI and control arms. RD expresses the absolute effect size when compared with the

relative risk or odds ratio, and this technique can be used when the binary outcome is zero in both study arms. Heterogeneity of the effects among studies was quantified using the I^2 statistic (I^2 > 50% indicates high heterogeneity). For the meta-analysis, we used the Review Manager software, version 5.4 (RevMan 5; Cochrane Collaboration, Oxford, United Kingdom).[22]

RESULTS

A total of 54 studies were retrieved from the selected databases. After eliminating duplicates and including studies that met the eligibility criteria, 12 studies were selected for assessment of full texts. Of these, 6 were excluded (Figure 1). Therefore, 6 RCTs involving 1,127 individuals, 577 and 550 of whom were in the intervention and control groups, respectively, were included in the meta-analysis,[12-16,23] as detailed in Table 1.

One study[12] included only adults (≥ 18 years of age; N = 123), and one[16] included 6-12 year-old children (N = 121). Four other studies included CF individuals ≥ 12 years of age. Duration of follow-up was 24 weeks in 4 studies, and 4-8 weeks in 2 others. Two studies reported a 96-week follow-up extension.[13,14] Most of the studies used an active comparator group (tezacafor/ivacaftor), and only 2[13,16] compared ETI to placebo (N = 526). The characteristics of each study, risk of bias, and quality of evidence are presented in Tables 1, 2, and 3, respectively. We considered that the risk of bias in the included studies to support the conclusions about treatment as serious. The quality of the evidence in the ETI group varied according to the outcome analyzed: exacerbations (low), FEV_1 (very low), BMI (very low), quality of life (very low), adverse events (moderate), and number of deaths (moderate).

The studies reported no deaths during the follow-up period. Therefore, it was impossible to estimate the

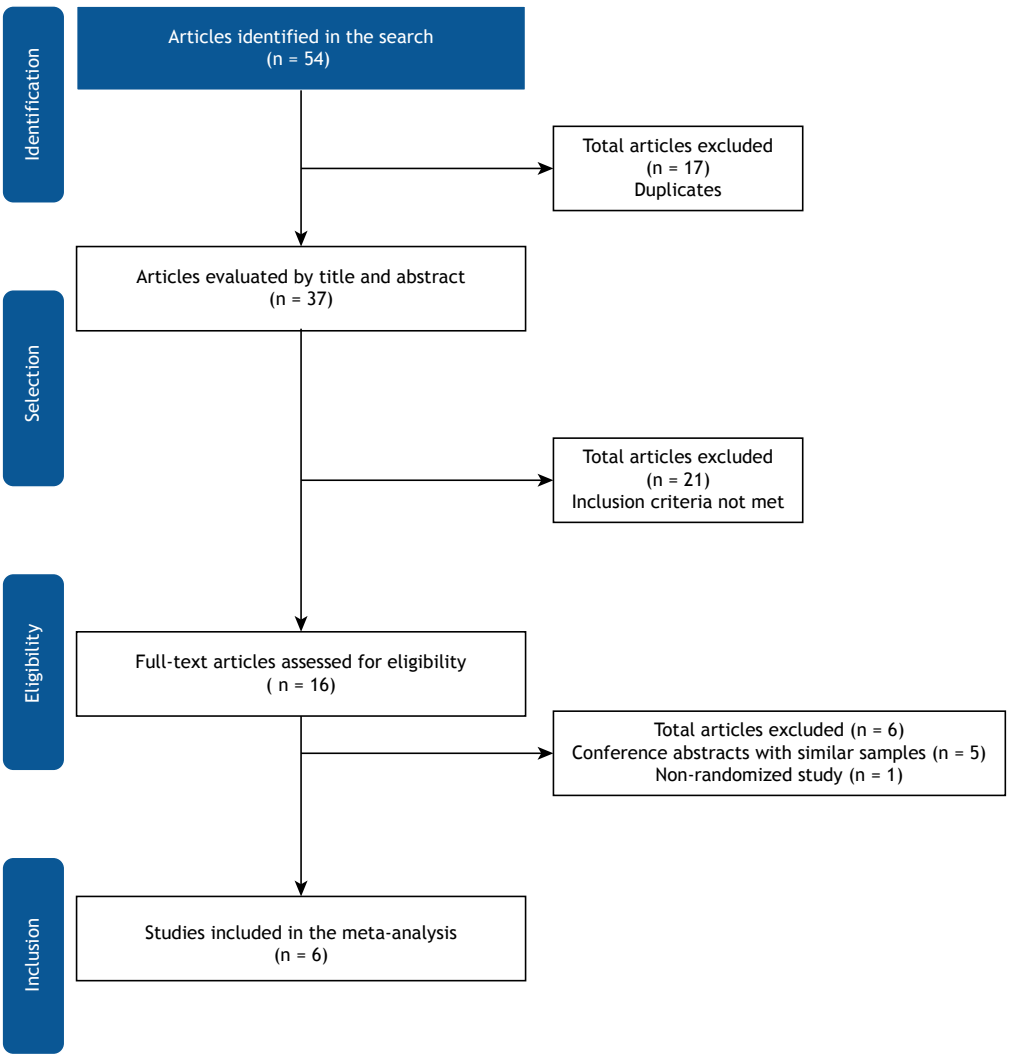


Figure 1. Flow diagram of study selection in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[18]

Table 1. Description of the studies included in the meta-analysis.

Study	Design	Population	Intervention (N)	Comparator (N)	Outcome	Duration
Barry et al.[23] (NCT04058353) North America, Europe, and Australia	Phase 3 double-blind RCT with active control arm	≥ 12-year-olds with CF and *F508del*-gating or *F508del*-residual function genotypes	ETI E: 200 mg once daily; I: 150 mg every 12 h; T: 100 mg once daily (N = 132)	TI or I I: 150 mg every 12 h; T: 100 mg once daily (N = 126)	FEV_1%, sweat chloride concentration, score on CFQ respiratory domain, adverse events	8 weeks
Heijerman et al.[14] (NCT03525548) Belgium, Netherlands, UK, and USA (NCT03525574-extension)	Phase 3 double-blind RCT with active control arm Open label extension	≥ 12-year-olds with CF and homozygous for *F508del* mutation, FEV_1 40-90%, stable CF	ETI E: 200 mg once daily; I: 150 mg every 12 h; T: 100 mg once daily (N = 55)	TI T: 100 mg once daily; I: 150 mg, every 12 h (N = 52)	FEV_1%, sweat chloride concentration, score on CFQ respiratory domain, adverse events	4 weeks 96-week extension
Keating et al.[12] (NCT03227471) USA, Netherlands, Belgium, and Australia	Phase 2 double-blind RCT with active control arm or placebo	≥ 18-year-olds with CF *F508del*-MF genotype patients were randomized to receive triple therapy or a triple placebo control Patients homozygous for the *F508del* mutation genotype were randomized to receive triple therapy or active control arm	*F508del*-MF genotype: ETI E: 50,100, or 200 mg once daily); I: 150 mg every 12 h; T: 100 mg once daily (n = 53) or VX-445 in triple combination with T and VX-561 (n = 22) Homozygous for *F508del*: ETI E: 200 mg/day p.o.; T: 100 mg/day; I: 150 mg every 12 h (n = 21) [64 patients received E 200 mg per day p.o.] (N = 96)	*F508del*-MF genotype: placebo (n = 12) or VX-445 in triple combination (n = 8) Homozygous for *F508del*: TI I: 150 mg every 12 h; T: 100 mg once daily (n = 7) (N = 27)	FEV_1%, score on CFQ respiratory domain, adverse events	4 weeks

Continue...▶

Table 1. Description of the studies included in the meta-analysis. (Continued...)

Study	Design	Population	Intervention (N)	Comparator (N)	Outcome	Duration
Mall et al.[16] (NCT04353817) Australia, Canada, Denmark, France, Germany, Israel, Netherlands, Spain, Switzerland, and UK	Phase 3 double-blind placebo-controlled RCT	6-12-year-olds with CF and *F508del*-MF genotypes, FEV_1 40-90%, stable CF	Children < 30 kg: E: 100 mg once daily; T: 50 mg once daily; I: 75 every 12 h Children ≥ 30 kg: E: 200 mg once daily; T: 100 mg once daily; I: 150 every 12 h (N = 60)	Placebo (N = 61)	FEV_1%, lung clearance index, sweat chloride concentration, score on CFQ respiratory domain, adverse events	24 weeks
Middleton et al.[13] (NCT03525444) USA, Europe, and Australia Extension (NCT03525574)	Phase 3 double-blind placebo-controlled RCT Open label-extension	≥ 12-year-olds with CF and heterozygous for the *F508del*-MF genotype, FEV_1 40-90%, stable CF	ETI E: 200 mg once daily; I: 150 mg every 12 h; T: 100 mg once daily (N = 201)	Placebo (N = 204)	FEV_1%, exacerbations, BMI, sweat chloride concentration, score on CFQ respiratory domain, adverse events	24 weeks 96-week extension
Sutharsan et al.[15] (NCT04105972) Australia, Belgium, Germany, and UK	Phase 3 double-blind RCT with active control arm	≥ 12-year-olds with CF and homozygous for *F508del*, FEV_1 40-90%, stable CF	ETI E: 200 mg once daily; I: 150 mg every 12 h; T: 100 mg once daily (N = 87)	TI I: 150 mg every 12 h; T: 100 mg once daily (N = 88)	FEV_1%, sweat chloride concentration, score on CFQ respiratory domain, adverse events	24 weeks

RCT: randomized controlled trial; CF: cystic fibrosis; E: elexacaftor; T: tezacaftor; I: ivacaftor; CFQ: Cystic Fibrosis Questionnaire; and MF: minimal function.

impact on mortality with a moderate quality of evidence. Results of the meta-analysis revealed a statistically significant improvement in the respiratory domain of the quality of life questionnaire (RD, +14.93; 95% CI, 9.98-19.89), with very low quality of evidence (Figure 2A); a statistically significant effect on FEV_1 in the ETI group (RD; +10.47%; 95% CI, 6.88-14.06], with very low quality of evidence (Figure 2B); and also a statistically significant difference in BMI (RD, +1.07 kg/m^2; 95% CI, −0.90 to 1.25), with very low quality of evidence (Figure 2C). We also observed a statistically significant reduction in the number of acute pulmonary exacerbations (RD, −0.16, 95% CI, −0.28 to −0.04), with low quality of evidence (Figure 3A), but no significant impact on the occurrence of adverse effects (RD, −0.03; 95% CI, −0.08 to 0.01), with moderate quality of evidence (Figure 3B).

DISCUSSION

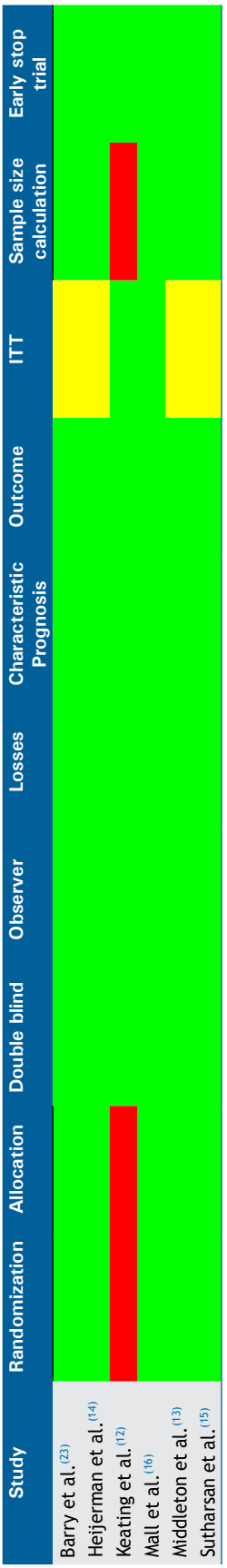
In this systematic review and meta-analysis regarding the efficacy and safety of the combination of three CFTR modulators (ETI) in patients with CF and at least one *F508del* allele, we found that treatment with ETI, compared with treatment with placebo or other CFTR modulators, reduced exacerbations and improved lung function, BMI, and quality of life. There were no significant differences in adverse events or mortality.

Our findings support the adoption of ETI combination therapy for patients with CF and at least one *F508del* allele, given that this combination led to substantial improvements in clinically significant, patient-centered outcomes, without a significant impact on adverse events. A previous systematic review, also including 6 studies, about the triple therapy for CF patients found similar results.[24] However, 1 of the studies included used a different combination of modulators (VX-659 instead of elexacaftor, combined with ivacaftor and tezacaftor),[25] and because the search was limited to December of 2021, it did not include the study by Mall et al.,[16] published in 2022 and included in our study. The similarity of the findings reinforces the robustness of data supporting the clinical effectiveness of ETI therapy.

Recent clinical practice guidelines by the Brazilian Thoracic Society addressing other common treatments for CF[17] did not include the ETI treatment, because the clinical questions were formulated before ETI therapy was available in Brazil. Therefore, this systematic review and meta-analysis complements the findings of the clinical practice guidelines[17] and offers robust information to the scientific literature that could support health care decisions in Brazil and in other countries. The magnitude of clinical impact observed with the ETI treatment in CF patients with at least one *F508del* allele was remarkable, and comparable to that observed with ivacaftor for patients with CFTR gating mutations.[26]

Our results are also in line with findings of recent observational studies on ETI in real life scenarios.[27,28]

Table 2. Risk of bias of the randomized clinical trials included in the meta-analysis.[a]



ITT: intention to treat. [a]Red: risk of bias; yellow: unclear; and green: without risk of bias.

Table 3. Quality of evidence regarding the use of elexacaftor+tezacaftor+ivacaftor triple combination in cystic fibrosis patients.

Certainty assessment							No of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Elexacaftor + tezacaftor + ivacaftor	Placebo or active control	Relative (95% CI)	Absolute (95% CI)		
Mortality												
6	randomized trials	serious[a]	not serious	not serious	not serious	none	0/577 (0.0%)	0/550 (0.0%)	not estimable	0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕⊕O Moderate	CRÍTICAL
Adverse events												
6	randomized trials	serious[a]	not serious	not serious	not serious	none	470/577 (81.5%)	464/550 (84.4%)	not estimable	0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕⊕O Moderate	CRÍTICAL
Quality of life												
6	randomized trials	serious[a]	serious[b]	not serious	serious[c]	none	577	550	-	mean 14.93 points higher (9.98 higher to 19.89 higher)	⊕OOO Very low	CRÍTICAL
Pulmonary exacerbations												
6	randomized trials	serious[a]	serious[b]	not serious	not serious	none	65/577 (11.3%)	165/550 (30.0%)	not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕OO Low	IMPORTANT
FEV_1												
6	randomized trials	serious[a]	serious[b]	not serious	serious[c]	none	577	550	-	mean 10.47 pp higher (6.88 higher to 14.06 higher)	⊕OOO Very low	IMPORTANT
BMI												
3	randomized trials	serious[a]	serious[b]	not serious	serious[c]	none	343	344	-	mean 1.07 kg/m² higher (0.9 lower to 1.25 higher)	⊕OOO Very low	IMPORTANT

pp: percentage points.
Explanations
a. Randomization and no mentioning of intention to treat
b. High heterogeneity
c. Large confidence interval

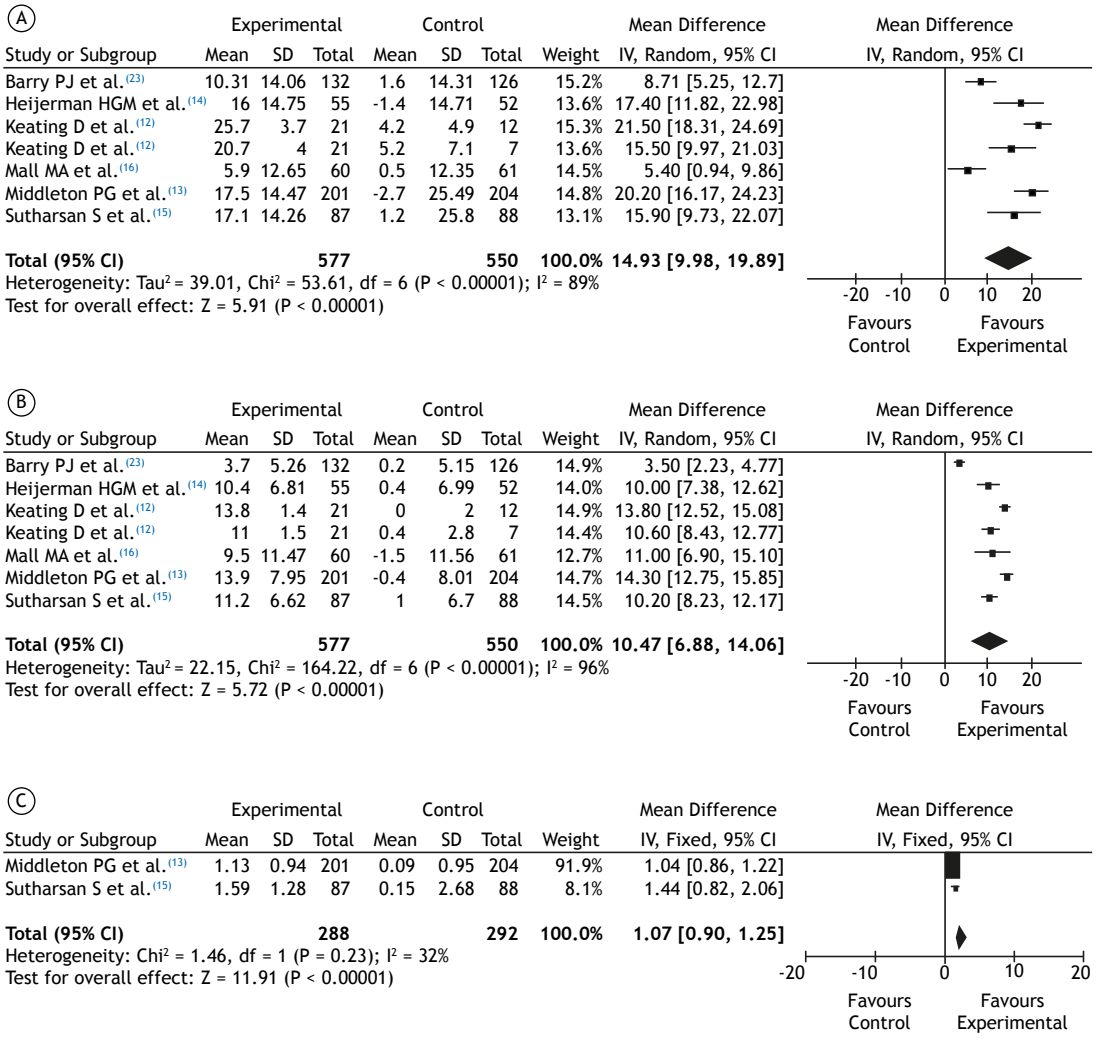


Figure 2. Forest plots of the included studies evaluating the efficacy of elexacaftor+tezacaftor+ivacaftor vs. placebo in individuals with cystic fibrosis and at least one *F508del* allele. In A, quality of life determined by the respiratory domain score of the Cystic Fibrosis Questionnaire respiratory domain; in B, FEV_1 in percentage of the predicted value; and, in C, BMI. IV: inverse of the variance; and df: degrees of freedom

A recently published interim analysis of a registry-based study reported the impact of ETI treatment for 2 years on more than 16,000 North American CF individuals.[27] Treatment with ETI was associated with significant and sustained improvements in lung function and reductions in acute pulmonary exacerbations and hospital admissions. Moreover, no new safety concerns were identified, and there was a 72% lower rate of mortality and 85% lower rate of lung transplantation in regard to the year before ETI availability.[27] Similar findings were described in a French cohort of 245 patients with CF and severely impaired lung function, who experienced decreases in long-term supplemental oxygen therapy, noninvasive ventilation, and enteral tube feeding requirements, in addition to a decrease in lung transplant listing.[28]

The combined data from the RCTs included in this meta-analysis indicate that the mean gain in lung function (FEV_1 in % of predicted value) with the ETI therapy was +10.4%. This result is clinically significant and superior to that of most of the therapies adopted to treat CF-related lung disease, such as dornase alpha (+5.8%)[29] and azithromycin (+6.2%),[30] and comparable to that of inhaled tobramycin for patients chronically infected with *Pseudomonas aeruginosa* (+10%).[31] This gain in lung function is even more impressive if we take into account that the average lung function of the current CF population included in the ETI studies has been much higher than it was in the past,[32] making those improvements of such magnitude even more remarkable. The efficacy results even in CF individuals with only one *F508del* allele combined with any minimal function mutation[13] are also remarkable and indicate that the minimum amount of functional CFTR needed to result in a significant clinical impact may be in fact around 10-30% of CFTR function, as previously estimated.[33]

The reduction of acute pulmonary exacerbations and improvements in the respiratory domain of quality of life questionnaires are very consistent across the studies;

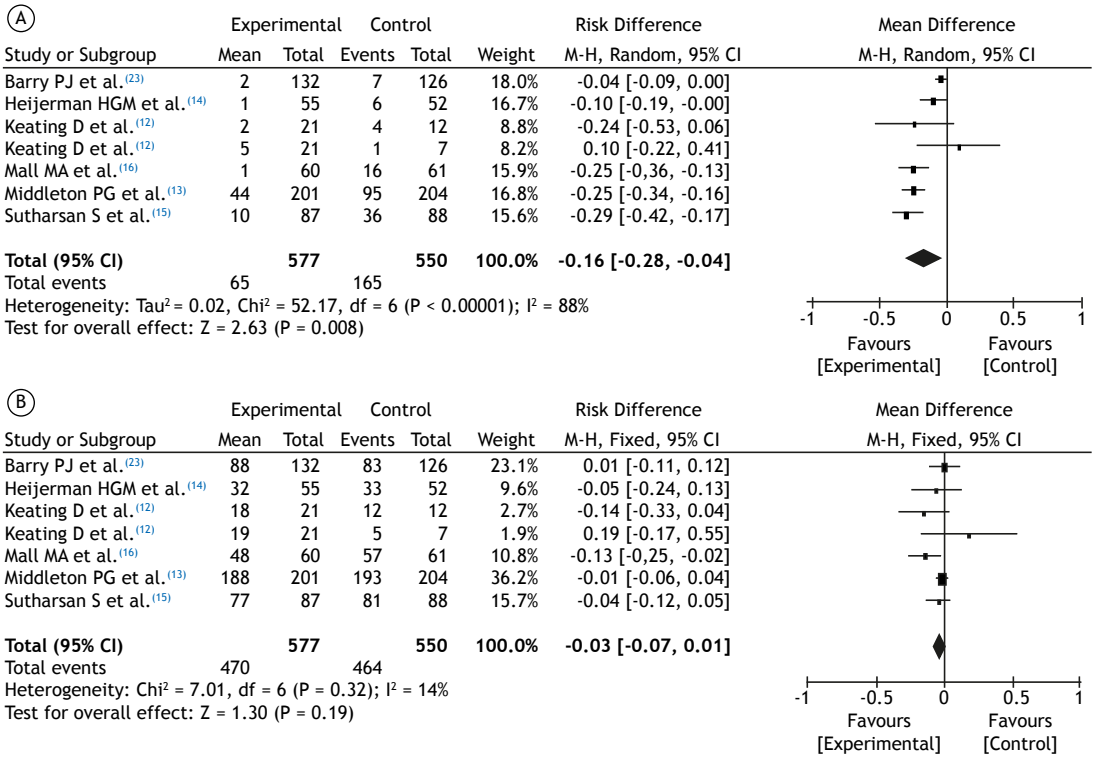


Figure 3. Forest plots of the included studies evaluating the efficacy of elexacaftor+tezacaftor+ivacaftor vs. placebo in individuals with cystic fibrosis and at least one *F508del* allele. In A, acute pulmonary exacerbations; and, in B, adverse events. M-H: Mantel-Haenszel (method); and df: degrees of freedom.

all of the 6 studies showed improvements in quality of life, and 5 showed reductions in the number of exacerbations. Acute exacerbations in CF are associated with several negative outcomes, such as an increase in the number of work or school days missed, weight loss, worse quality of life, and increased health care costs,[34] and, therefore, are a very important patient-centered outcome in CF. Although none of the included studies was designed or powered to estimate the effect of ETI on mortality, the finding that ETI reduces exacerbations underscores the potential impact of this therapy on long-term survival. We found that ETI adverse events were similar to those of other treatment options or placebo. Most of the studies reported only mild and transient adverse effects, the most worrisome ones being rashes, liver function alterations, and psychiatric effects such as anxiety.[35] Such effects were described as reversible with temporary drug discontinuation, and, in most cases, they did not result in permanent discontinuation of treatment, allowing its continuation after some days or weeks.[35]

Our findings have important implications for patients with CF, given that other treatment options are scarce. Initial studies of combinations of two drugs for CF patients with *F508del* CFTR mutations showed a modest impact on lung function or sweat chloride measurements,[36] while the use of lumacaftor as the corrector resulted in safety concerns.[37] However, the combination of lumacaftor and ivacaftor was the only option for young (2-5 years of age) CF individuals homozygous for *F508del* until May of 2023, when ETI therapy was approved by the Food and Drug Administration to treat these patients after the publication of results of a phase-3 open-label study.[38] Since early lung disease do occur in some patients with a significant clinical impact,[39] more studies on CFTR modulators in younger CF children are imperative.

Our study has several limitations. First, only RCTs were included. New data stemming from real-life studies are significantly expanding the knowledge about the effectiveness of new treatments in the CF population,[27,40-42] and such studies should be considered in future analyses on health care benefits of these interventions. Second, only 6 studies were included. However, CF is a rare disease, and ETI is a new and expensive medication, which has been available only for a few years. Third, we were underpowered to detect the impact of ETI on mortality since all of the studies followed patients for just a few weeks/months and typically reported only few or no deaths. Additionally, data regarding benefits and risks of using ETI in CF individuals with preserved lung function and good quality of life were limited. Finally, our study does not include a cost-effectiveness analysis.

The current annual cost per patient of the ETI treatment paid by countries with negotiated agreements is more than US$250,000, which is very expensive for governments and private health care insurers in

low- and middle-income countries such as Brazil.[43] As negotiations between governments and the company are occurring, our findings highlight the effectiveness of ETI in improving patient-centered outcomes and may help inform future public health policies to provide evidence-based care for individuals with CF living in such countries, changing the landscape of long-term survival in CF.[44]

AUTHOR CONTRIBUTIONS

LVRFSF and RAA: study conception. CRT, JCF, and SET: data collection and analysis. All of the authors contributed to drafting and reviewing the manuscript and approved the final version.

CONFLICTS OF INTEREST

None declared.

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