Sex-based differences in cystic fibrosis pulmonary exacerbations: Subanalysis of the Standardized Treatment of Pulmonary Exacerbations–2 cohort

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Background: Data have shown that women and girls with cystic fibrosis (CF) have higher morbidity and mortality than men and boys, yet evaluations of differences in clinical trials outcomes according to sex in CF are limited. Using the Standardized Treatment of Pulmonary Exacerbations–2 (STOP2) cohort, we examined sex-based differences in pulmonary exacerbation (PEX) outcomes in people with CF treated with intravenous (IV) antibiotics.

Methods: STOP2 was a multi-center, randomized, controlled, clinical trial of treatment duration in adults with CF who received IV antibiotics for a PEx conducted from July 2016 through January 2020. Participants were randomized to 10 vs 14 days of antimicrobials (early robust responder) if they demonstrated predefined lung function and symptom improvements after 7 to 10 days of treatment or were randomized to 14 vs 21 days (non-early robust responders). Aligning with STOP2, our primary outcome was the difference between the sexes in absolute change in percentage predicted forced expiratory volume in 1 second (FEV1pp) from treatment initiation (Visit 1) to 2 weeks after IV antibiotics (Visit 3) using multivariable linear regression models adjusted for trial stratification variables and a priori demographic and clinical characteristics. Secondary endpoints included Chronic Respiratory Infection Symptom Score (CRISS), weight, time to next PEx, and adverse events.

Results: Nine hundred eighty-two participants (496 [50.5%] female) were randomized and constituted the intention to treat population. Overall, women and girls were more likely to have had an IV-treated PEx in the prior year, have higher maximum and average baseline FEV1pp in the prior year, and more likely to be prescribed steroids during STOP2 than men and boys. We found no sex differences in mean FEV1pp decline from 6 months before the study baseline to Visit 1 (difference 1.16; 95% CI, −0.07–2.40). Women and girls had a significantly higher mean FEV1pp than men and boys (52.7% vs 47.0%, p < 0.001) at Visit 1, but there was no difference in FEV1pp change from Visit 1 to Visit 3 between (difference −0.73; 95% CI, −1.78–0.33). Similarly, CRISS was significantly higher (worse) for women and girls than for men and boys at study enrollment (52.3 vs 49.2, p < 0.001). There was no statistically significant difference in CRISS change from Visit 1 to Visit 3 between the sexes (difference −0.27; 95% CI, −1.94–1.41). Women and girls gained less weight from Visit 1 to Visit 3 (difference between groups −0.73 kg; 95% CI, −1.04, −0.42) and were at greater risk of a subsequent IV-treated PEx (HR 1.26; 95% CI, 1.07–1.47) than men and boys. We found no difference in adverse events (any or serious) according to sex. Results were generally consistent within the early robust responder and non-early robust responders study arms.

Conclusions: Our results suggest that there are sex-related differences in PEx presentation. Women and girls started with a better lung function at treatment initiation yet reported worse respiratory symptoms than men and boys. Although we found no sex difference in lung function or respiratory symptoms after IV antibiotic treatment, female sex was associated with greater risk for future IV-treated PEx. Understanding sex disparities in CF is a priority for the CF community and needs to be further explored in relation to highly effective modulator therapy.

Acknowledgements: This work was supported by the Cystic Fibrosis Foundation (MONTEMQ020).

Patent foramen ovale and oxygenation in patients with cystic fibrosis

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Background: The prevalence of patent foramen ovale (PFO) in the general population is estimated to be around 24% [1]. The prevalence of PFO in people with cystic fibrosis (PwCF) is unknown, but potentially high pulmonary artery pressure in CF could increase shunting through an existing PFO. This study assessed the prevalence of PFO in PwCF and evaluated potential associations with hypoxemia, pulmonary function, and mortality.

Methods: We conducted a retrospective study of PwCF who attended the adult CF center at the University of Utah and had an echocardiogram with bubble study performed. For each PwCF with an echocardiogram with bubble study, we identified 1 or 2 non-CF control patients who were matched in age and sex and had had a similar study performed within six months. We used logistic regression and proportional hazards modeling to understand the impact of a PFO in CF.

Results: Of 64 people with CF who had a previous echocardiography with bubble study performed, 35 (55%) had a PFO. Of 93 non-CF age- and sex-matched controls who had echocardiograms with bubble studies performed at a similar time, 32 (34%) had a PFO. In age- and sex-adjusted logistic regression, PwCF were more likely to have a PFO (OR 2.4, p = 0.01). PwCF with PFO were more likely to have hypoxemia (OR 5.1, p = 0.01). With a linear regression model, we did not find an association between PFO and lower percentage predicted forced expiratory volume in 1 second (FEV1pp).

Conclusions: Our study showed that PFO is more common in PwCF than in those without (Figure 1). PwCF with a PFO are more likely to need supplemental oxygen but do not have a lower FEV1pp, suggesting that PFOs are independently associated with hypoxemia and need for supplemental oxygen. We recommend echocardiogram with bubble study at least once in PwCF who require supplemental oxygen. Further study is needed to understand the impact of a PFO in CF.