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Gender does not influence the response to the combination of salmeterol and fluticasone propionate in COPD ☆

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Summary The prevalence of chronic obstructive pulmonary disease (COPD) in women is increasing worldwide. Women may have greater susceptibility to COPD progression than men, and differences in efficacy and safety of respiratory medications by gender are largely unexplored. We aimed to determine whether the response to treatment in women with COPD differed from men in a large, 1-year double-blind trial ('TRISTAN'). In a sensitivity analysis, we compared 539 male and 180 female COPD patients, who were randomized to the salmeterol/fluticasone combination 50/500 mcg bid or placebo for 12 months. Combination therapy improved pre-treatment FEV_1 significantly more than placebo in women by 152 ml (95% confidence interval 95–208) and in men by 127 ml (94–159). Similarly, a reduction in COPD exacerbation rates of 31% in women (9–48%) and of 23% in men (8–35%) was observed. Combination therapy reduced COPD exacerbations requiring treatment with oral corticosteroids by 36% in women and by 41% in men. Finally, combination treatment produced a better improvement in health status than placebo with a decrease in the SGRQ scores in women by −2.3 (−4.6 – 0.1) and in men by −2.1 (−3.5 to −0.8). No gender interaction was found for any outcome. Treatments were well tolerated with no difference in the frequency of adverse events in women and men. In this trial, therapy with the salmeterol/fluticasone combination produced significant improvements compared to placebo on all main endpoints and the magnitude of these improvements was similar for both men and women.

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Introduction

In 2000, for the first time, the number of women dying from chronic obstructive pulmonary disease (COPD) in the US surpassed the number of men dying from COPD.[1] It is forecasted that this increase in female COPD will be observed elsewhere.[2,3] On average, women smoke less and do not inhale tobacco as frequently as men. It has therefore been hypothesized that women are more susceptible to the deleterious effects of smoking in their lungs, and for a given history of smoking women may be more likely than men to develop COPD.[4,5] Gender differences in the presentation of respiratory disease have been recently and comprehensively reviewed,[6] and it is now well accepted that there are differences between the sexes in the presentation and pathophysiology of COPD, as recognized in other diseases.[7] However, less effort has been dedicated to examine gender effects in the efficacy of respiratory medication and, to our knowledge, gender effects in COPD medication have not been investigated. The TRISTAN trial is a multi-centre, randomized, double-blind, placebo-controlled, parallel-group study of 1465 COPD patients treated with either salmeterol 50 mcg bd (an inhaled long-acting β_2-agonist), fluticasone 500 mcg bd (an inhaled corticosteroid), salmeterol/fluticasone combination 50/500 mcg bd or placebo for 12 months.[8] By using the combination and placebo arms of this trial, we investigated whether combination treatment is equally efficacious in women and men.

Methods

The methods and the primary results of the TRISTAN trial can be found elsewhere.[8] Briefly, it was designed to compare the efficacy of salmeterol/fluticasone propionate combination (SFC; 50/500 mcg bd) with salmeterol alone (50 mcg bd), fluticasone propionate alone (500 mcg bd) and placebo, and to compare safety in all treatment groups. Main endpoints were pre-bronchodilator FEV_1, rate of exacerbations, and Health Status as determined using St George's Respiratory Questionnaire. Inclusion criteria were COPD (ERS definition), age 40–79 years, >10 pack-years, pre-bronchodilator FEV_1 25–70% predicted, FEV_1/FVC <70%, poor reversibility (<10% predicted FEV_1) and chronic bronchitis with exacerbations in the last 3 years.

Exclusion criteria were current diagnosis of asthma, eczema, allergic rhinitis, use of systemic steroids, antibiotics or change in COPD medication during the last 4 weeks. Permitted COPD medications were salbutamol (relief medication), anticholinergic agents, and oral corticosteroids or antibiotics in short courses for exacerbation treatment, mucolytics (acetylcysteine), sodium cromoglycate (nedocromil sodium, ketotifen), and LTOT. Non-permitted medications were oral short-acting ß$_2$-agonists, other inhaled corticosteroids, other long-acting β_2-agonists and combination bronchodilators (Combivent, Berodual, Duovent). The study conclusion was that combining inhaled long-acting β_2-agonist and corticosteroid therapy produces significantly better symptom control and lung function at no greater risk of side effects than using either component alone.

In this analysis we focused on the comparison of the salmeterol/fluticasone combination to placebo arms only. Our null hypothesis was that the beneficial effects of salmeterol/fluticasone combination versus placebo in terms of pre-bronchodilator FEV_1, rate of exacerbations (all and severe exacerbations), and health status are equally good in women and men. As per consensus, rejection of the null hypothesis would happen if a 20% difference in a quantitative variable (FEV_1, number of exacerbations, or SGRQ) by gender was found. Repeated measures to analyse FEV_1 and SGRQ, and Poisson generalized linear model analysis of exacerbations were conducted. Covariates included smoking status, age, baseline FEV_1, and centre. Treatment, gender, and treatment by gender terms were fitted in the model, and the predicted values for men and women were obtained, along with confidence intervals, and *P*-values of the significance of the effect in both men and women.

Results

The TRISTAN trial was conducted at 196 centres in 25 countries and recruited 1974 patients, of whom 1465 received treatment. Of the 719 COPD patients randomized to salmeterol/fluticasone combination or placebo, 180 (25%) were women. There were no differences by gender regarding duration of COPD disease, withdrawal after randomization, previous use of LABA, reversibility, FEV_1% predicted, or health status. Females were younger, more frequently current smokers but with less pack-years, more frequent previous users of ICS, had smaller lung volumes and used more frequently relief medication than men (all $P<0.05$). With the possible exception of smoking, the observed statistically

Table 1 Demographic and baseline characteristics of the Tristan participants randomized to salmeterol/fluticasone combination or placebo, in women and men.

Characteristic	Females	Males	*P*-values*
Number	180	539	
Withdrawal after randomization	61 (34%)	168 (31%)	0.498
Age mean (SD)	61 (8.6)	64 (8.5)	<0.001
Duration of disease			
<5 years	52 (29%)	124 (23%)	
5–10	69 (38%)	201 (37%)	
10–15	30 (17%)	110 (20%)	
⩾15 years	29 (16%)	104 (19%)	0.301
Current smoker *n* (%)	101 (56%)	256 (47%)	0.045
Mean pack years smoked (SD)	35 (18)	45 (23)	<0.001
Previous ICS use *n* (%)	107 (59%)	259 (48%)	0.008
Previous LABA use *n* (%)	67 (37%)	220 (41%)	0.394
Pre-treatment FEV_1 ml (SD)	1020 (392)	1376 (501)	<0.001
Pre-bronchodilator FEV_1% pred (SD)	45.0 (14.3)	44.3 (14.2)	0.572
Reversibility (% predicted FEV_1) (SD)	4.42 (5.96)	4.89 (4.07)	0.180
Post-bronchodilator FEV_1 ml (SD)	1117 (407)	1494 (511)	<0.001
Pre-treatment FVC ml (SD)	1866 (559)	2737 (775)	<0.001
Mean total SGRQ score (SD)	47.4 (15.6)	47.0 (16.3)	0.791
Median use of relief med./day	3.0	2.1	0.005
Mean no. awakenings/week (SD)	2.9 (4.8)	3.1 (5.2)	0.664

ICS: inhaled corticosteroids; LABA: long-acting β_2-agonist; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; SGRQ: St. George's Respiratory Questionnaire; SD: standard deviation.
**P*-values for the comparison female versus male.

significant differences in baseline characteristics by gender were of little clinical relevance (Table 1).

The differential dropout after randomization was almost identical in women and men. Only 26% of women randomized to combination treatment withdrew after randomization compared to 41% women randomized to placebo. The same pattern was observed in men, 24% versus 38%, respectively.

Combination therapy improved pre-treatment FEV_1 significantly more than placebo in women by 152 ml, (95% Confidence interval 95–208) and in men by 127 ml, (94–159). This improved pre-treatment FEV_1 was equivalent in women and men (*P*-value 0.455 for the gender interaction) (Table 2). Similarly, a reduction in COPD exacerbation rates of 31% in women (9–48%) and of 23% in men (8–35%) was observed, with a non-significant *P*-value 0.520 for the gender interaction (Fig. 1). In addition, combination therapy reduced COPD exacerbations requiring treatment with oral corticosteroids, the yearly rate being reduced by 36% in women compared to placebo (9–55%) and by 41% in men (25–53%), *P*-value 0.695 for the gender interaction (Fig. 2). Combination treatment produced a significantly better improvement in health status than placebo with a decrease in the SGRQ scores in women by −2.3 (−4.6 to 0.1) and in men by −2.1 (−3.5 to −0.8). This improved health status was again equivalent in women and men, *P*-value 0.904 for the gender interaction.

Finally, the frequency and severity of adverse events were analysed by gender (Table 3). Combination treatment was well tolerated with no significant difference between women and men in the number of patients reporting an adverse event during treatment. The exception was for an increased prevalence of oropharyngeal candidiasis in both women and men randomized to combination treatment. Throat irritation in women on combination treatment was frequently reported (11%).

Although not shown in this paper, there was again no gender interaction in the comparison versus placebo of the treatment arms with single components salmeterol 50 mcg and fluticasone combination 500 mcg twice.

Discussion

We did not find differences between women and men with COPD in the efficacy and safety outcomes in a trial comparing the salmeterol/fluticasone propionate combination versus placebo. Improvements in pulmonary function, frequency of

Table 2 Effect of Combination treatment versus placebo over 52 weeks on trial outcomes pre-treatment FEV_1 and health status, by gender.

Outcome measures	Females ($n = 180$)		Males ($n = 539$)	
	Combination	Placebo	Combination	Placebo
Pre-treatment FEV_1 ml				
N	84	92	261	261
Baseline, raw mean (SE)	994 (384)	1042 (402)	1409 (534)	1336 (468)
Adjusted, mean (SE)	1397 (21)	1245 (21)	1405 (12)	1279 (12)
Treatment difference (CI)	152 (95, 208)		127 (94, 159)	
P-value	<0.001		<0.001	
Gender interaction 0.455				
SGRQ total score				
N	78	82	242	236
Baseline, raw mean (SE)	46.2 (16.7)	48.5 (14.5)	47.3 (15.5)	46.2 (16.8)
Adjusted, mean (SE)	43.2 (0.9)	45.5 (0.9)	44.7 (0.5)	46.9 (0.5)
Treatment difference (CI)	−2.3 (−4.6, 0.1)		−2.1 (−3.5, −0.8)	
P-value	0.055		0.002	
Gender interaction 0.904				

Combination: salmeterol/ fluticasone combination (50/500 mcg twice daily); FEV_1: forced expiratory volume in one second; SE: standard error; CI: 95% confidence interval; SGRQ: St. Georges' Respiratory Questionnaire: a negative value represents an improvement in health status.

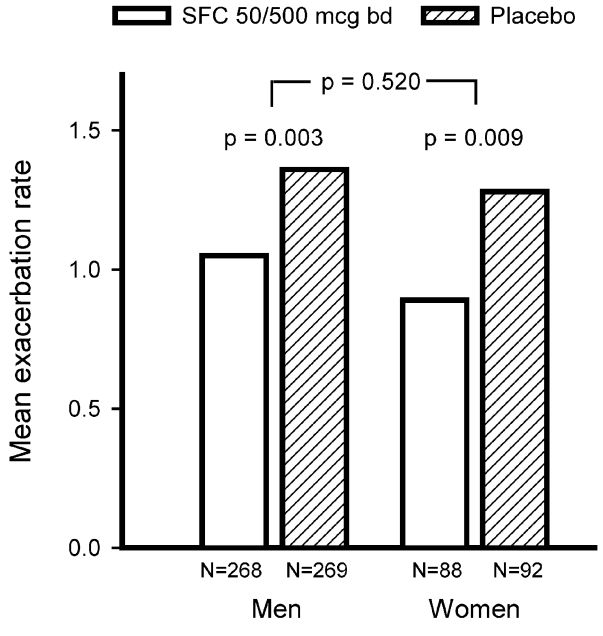

Figure 1 Total exacerbation rate.

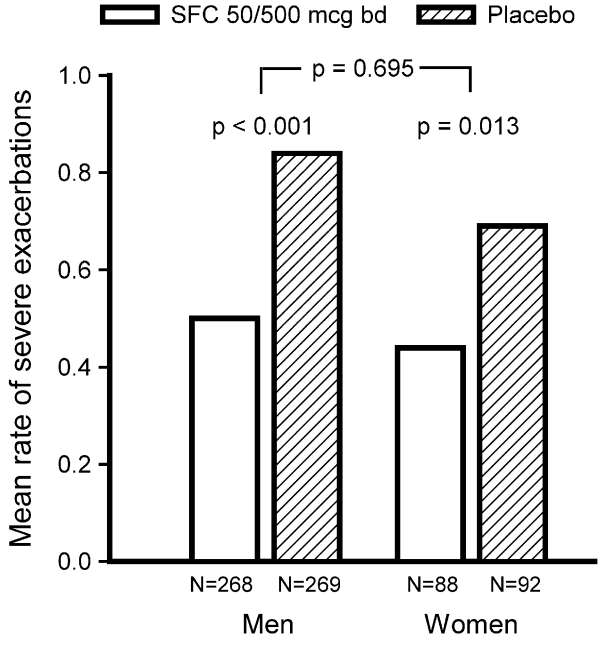

Figure 2 Rate of exacerbations requiring treatment with oral corticosteroids.

exacerbations and health status were of identical direction and similar magnitude in both sexes. Similarly, safety results were of similar magnitude in both arms in women and men, although women reported more frequently adverse events than men. These results are comforting for the way medicine is usually practiced and may stimulate further analyses on respiratory drugs and gender.

From an epidemiological perspective, COPD is transforming from a disorder seen in elderly smoking men, to affect more women and probably at a younger age.[9] Regretfully, women were systematically excluded from RCTs until very recently. Only since 1998 the FDA requested that all NIH funded safety and efficacy trials should include women. Recent non-pharmacological

Table 3 General and most common drug-related adverse events during treatment with the salmeterol/fluticasone combination or placebo, by gender.

Event, *n* (%)	Females ($n = 180$)		Males ($n = 539$)	
	Combination	Placebo	Combination	Placebo
N (%)	88	92	270	269
Any adverse event	76 (86%)	75 (82%)	209 (77%)	208 (77%)
Serious adverse event	12 (14%)	12 (13%)	50 (19%)	42 (16%)
Drug-related adverse event	13 (15%)	15 (16%)	45 (17%)	34 (13%)
Withdrawn due to adverse event	10 (11%)	21 (23%)	31 (11%)	45 (17%)
Candidiasis mouth/throat	7 (8%)	3 (3%)	20 (7%)	3 (1%)
Nausea and vomiting	1 (1%)	1 (1%)	0	2 (<1%)
COPD exacerbation	49 (56%)	53 (58%)	127 (47%)	139 (52%)
Lower respiratory infection	9 (10%)	5 (5%)	22 (8%)	14 (5%)
Throat irritation	10 (11%)	1 (1%)	12 (4%)	10 (4%)
Headaches	4 (5%)	4 (4%)	11 (4%)	14 (5%)

interventions in COPD have explored on gender differences with inconclusive results.[10–12] Goodman et al.[13] have found that women are less likely than men to perform acceptable metered-dose inhaler use but this has little relevance to the present study where we used the Diskus device. Recent placebo-controlled tiotropium trials have been analysed with focus on the influence of gender on outcomes. Findings have only been reported as abstract[14] but seem to indicate less effect of tiotropium on exacerbations in women.

In asthma, Mohamed et al.[15] studied race and gender effects on salbutamol pharmacodynamics in 30 patients with moderate asthma (15 blacks, 15 whites, 16 men, 14 women). No important racial or gender differences in salbutamol-evoked FEV_1 or percent-predicted FEV_1 were evident, although females tended to be more sensitive compared to males. Convery et al.[16] investigated in a small sample of patients the effect of FP and gender on airway responsiveness, and found a better outcome in asthmatic men. The multiple linear regression analysis showed that the magnitude of the steroid effect was significantly greater in males than in females (3.2 versus 1.2 doublings, respectively, of the PD_{20} geometric mean). They concluded that inhaled corticosteroids caused a steadily increasing improvement in airway responsiveness over a 6-week period, which was better in men but lost almost immediately on treatment cessation. These findings may, however, reflect that airway responsiveness in general differs between men and women. Leynaert et al.[17] found that young women were more hyperresponsive than men. When airway hyperresponsiveness was defined as $PD_{20} < 4$ mg/ml methacholine, 37.3% of women were hyperresponsive in contrast to 18.6% of men.

Gender analyses of drugs in respiratory disease in general, and in COPD in particular, are relevant. Differences in efficacy and safety of respiratory drugs might indicate differences between the sexes in the presentation and pathophysiology of COPD, as recognized in other diseases. Not only do women represent half of mankind, but they also take more than their share of the increasing COPD burden worldwide. Chapman et al.[18] elegantly reported that North American primary care doctors underdiagnosed COPD frequently, but reluctantly diagnosed COPD in women even with evidence of objective airflow obstruction.

Our study was powered to detect a 100 ml difference in FEV_1 in the total intention-to-treat population. For this reason power to detect gender differences in the effect of the salmeterol/fluticasone combination therapy is somewhat limited as reflected in the 95% confidence intervals for treatment effects shown in Table 2. With the point estimates given, however, we feel confident that no major gender differences are present.

To conclude, it appears that in this trial the salmeterol/fluticasone combination therapy produced significant improvements compared to placebo on all main endpoints in female and male COPD patients. There was no significant treatment interaction with gender and the magnitude of these improvements was similar for both men and women. The search for gender interactions should be explored in other respiratory medications.

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