

Asthma Exacerbation Severity Is Greater for Women than for Men

Olga Ryan¹, Rohit Katial¹, Ian Hirsch², James L. Kreindler³

¹AstraZeneca, Denver, CO, United States; ²AstraZeneca, Gaithersburg, MD, United States; ³AstraZeneca, Wilmington, DE, United States

Abstract

Rationale: Although asthma prevalence is greater for women than men, less is known about their comparative disease severity.

Methods: This *post-hoc* analysis of pooled data from SIROCCO (48 weeks; *Lancet* 2016;388:2115–27) and CALIMA (56 weeks; *Lancet* 2016;388:2128–41) examined asthma exacerbation severity for female and male patients with baseline blood eosinophil counts (BEC) ≥ 300 cells/ μ L. Patients were 12–75 years of age and had high-dosage ICS/LABA use and ≥ 2 previous exacerbations. Patients received benralizumab 30 mg subcutaneously every 4 weeks (Q4W) or every 8 weeks (first three doses Q4W) or placebo.

Results: Mean IgE concentrations were less for women (514 IU/mL, n=969) than men (771 IU/mL, n=568). BEC were similar between women and men (470 and 480 cells/ μ L, respectively). A smaller percentage of women than men had atopic asthma (57.9% vs. 66.9%). Asthma reversibility was 26.4% for women and 25.0% for men. Baseline exacerbation rates for women and men were 2.9 and 2.8, respectively. More women than men had ≥ 3 exacerbations (41.5% vs. 36.1%). More women than men had exacerbations leading to hospitalization (1 exacerbation: 14.9% vs. 10.9%; 2 exacerbations: 7.5% vs. 6.2%), or emergency department visits (1 exacerbation: 8.4% vs. 7.0%; 2 exacerbations: 6.1% vs. 1.9%). More women than men (4.0% vs. 2.8%) required mechanical ventilation. Differences in comorbidities were also observed. Exacerbation reductions with benralizumab were similar between women and men.

Conclusions: Women and men responded similarly to benralizumab, although women had more severe disease, were less likely to have atopic asthma, and had lesser IgE concentrations.

Rationale and Background

- Asthma incidence, prevalence, and severity differ by sex throughout the life span^{1–3}
 - Asthma is more prevalent in boys compared with girls, (9.5% vs. 7.3%, respectively),^{1–3} with prevalence switching post puberty and greater in adult women (9.3% vs. 6.4%)^{2–3}
 - Health care resource utilization, hospitalizations, emergency department visits, and ambulatory care are greater for boys than girls (in children ≤ 14 years of age); conversely, asthma exacerbation rate (47.8% vs 42.2%), inpatient hospitalizations (58.7% vs 41.3%), emergency department visits (60.5% vs 39.4%), and mortality (14.4% vs 13.8%) are greater for adult women than men^{1,3–5}
 - Female sex is also associated with poorer disease control and risk for severe asthma exacerbations^{6,7}
- Despite greater morbidity and disability, women demonstrate better lung function and show no differences in physician-assessed asthma severity compared with men^{8,9}
- Although women have more severe disease, they are less likely to have atopic asthma and have lesser immunoglobulin (IgE) concentrations compared with men^{1,10}
- Eosinophilic inflammation of the airways affects approximately half of all patients with asthma, with similar eosinophil counts commonly seen in men and women^{11–12}
- Elevated baseline blood eosinophil counts (BEC), but not serum IgE concentrations, are associated with increased disease severity, exacerbation frequency, and health care resource use in patients with severe, uncontrolled asthma^{11–15}

- Sex differences have been linked to immunologic and sex hormone concentrations^{1,16,17}
 - Possible sex-specific asthma treatment has been suggested, with men and women requiring treatment modalities that act through different mechanisms¹⁸
- Despite well-established data regarding sex-related differences in asthma prevalence and severity throughout the life span, additional clinical data are needed to evaluate the sex impact of asthma in women and men and comparative disease severity and treatment response^{1,19}
- Benralizumab is a humanized, afucosylated, interleukin-5 α -directed cytolytic monoclonal antibody that induces direct, rapid, and nearly complete depletion of eosinophils via enhanced antibody-dependent cell-mediated cytotoxicity²⁰ and is approved in the US, Europe, and other countries for the add-on maintenance treatment of patients with severe asthma and an eosinophilic phenotype^{21,22}
- The results of the SIROCCO (NCT01928771)²³ and CALIMA (NCT01914757)²⁴ Phase III trials of benralizumab demonstrated that benralizumab 30 mg every 8 weeks (first three doses every 4 weeks) significantly reduced asthma exacerbations and improved lung function for patients with severe, uncontrolled asthma with baseline BEC ≥ 300 cells/ μ L receiving high-dosage ICS/LABA compared with placebo^{23,24}
 - ICS/LABA therapy combination budesonide/formoterol provides similar clinical benefits for patients of both sexes²⁵
 - Pooled analyses demonstrated that when added to high-dosage ICS/LABA therapy, benralizumab provided additional benefit for patients with severe uncontrolled asthma and at least 2 exacerbations in the previous year across the spectrum of baseline BEC, with exacerbation rates being reduced more in patients with increased blood eosinophil thresholds and greater exacerbation history^{26–28}
 - Oral corticosteroid (OCS) use, nasal polyposis, pre-bronchodilator FVC $< 65\%$ of predicted, 3 or more exacerbations in the previous year, and age at diagnosis ≥ 18 years were also associated with enhanced responsiveness to benralizumab treatment for reducing exacerbations and increasing lung function for the overall patient population and for those with baseline BEC ≥ 300 cells/ μ L²⁹
 - Benralizumab has also demonstrated similar clinical benefit for both men and women with severe eosinophilic asthma (elevated BEC), with similar consistent reductions in exacerbation risk and improvements in lung function, regardless of IgE concentrations (Table 1)^{13,27}

Table 1. Effects of Benralizumab for Patients with Severe Asthma: Pooled Subgroup Analysis for Women and Men from the High-Dosage Inhaled Corticosteroid Treatment Cohort with Baseline Blood Eosinophil Counts ≥ 300 cells/ μ L Enrolled in SIROCCO and CALIMA²⁷

	Benralizumab Every 4 Weeks Rate Ratio (Treatment/Placebo; 95% CI)	Benralizumab Every 8 Weeks Rate Ratio* (Treatment/Placebo; 95% CI)
Effects of Benralizumab Treatment on Annual Exacerbation Rate^b		
Women	0.63 (0.50–0.79)	0.59 (0.46–0.75)
Men	0.51 (0.37–0.71)	0.56 (0.41–0.78)
Effects of Benralizumab Treatment on FEV₁; Change from Baseline to End of Treatment (L)^c		
Women	0.101 (0.028–0.175)	0.095 (0.021–0.170)
Men	0.135 (0.043–0.227)	0.206 (0.115–0.297)

*30 mg every 8 weeks (first three doses every 4 weeks)

^bCalculated using a negative binomial model, with adjustment for treatment, study code, region, oral corticosteroid use at time of randomization, and prior exacerbations

^cCalculated using a mixed-effects model for repeated measures analysis with adjustment for treatment, study code, baseline value, region, oral corticosteroid use at time of randomization, visit, and visit \times treatment

- To further assess reported sex differences in asthma characteristics, data were analyzed from the SIROCCO and CALIMA trials to determine how baseline characteristics differed between the sexes with severe eosinophilic asthma (Poster 301, AAAAI 2019) and concluded that baseline characteristics were similar between women and men enrolled with baseline BEC ≥ 300 cells/ μ L³⁰
 - The current analysis is a continuation of the previous analysis to determine asthma exacerbation severity for men and women with baseline BEC ≥ 300 cells/ μ L and the effect of sex on treatment response

Aim

- In this *post-hoc* analysis of pooled data from SIROCCO (48 weeks)²³ and CALIMA (56 weeks),²⁴ we examined asthma exacerbation severity for men and women with baseline BEC ≥ 300 cells/ μ L

Methods

- Patient sex was a pre-specified subgroup for analyses of the primary endpoint in each study; however, this analysis of pooled baseline data from SIROCCO (48 weeks) and CALIMA (56 weeks) is *post hoc*
- Patients in the SIROCCO and CALIMA studies were aged 12 to 75 years, were receiving high-dosage ICS/LABA, and had experienced ≥ 2 exacerbations in the year before study entry
- Patients in both studies received benralizumab 30 mg subcutaneously every 4 weeks or every 8 weeks (first three doses every 4 weeks) or placebo
- Patients with baseline BEC ≥ 300 cells/ μ L were included in these analyses
- No *a priori* formal statistical analyses were tested

Results

- Of 1,537 patients enrolled in SIROCCO/CALIMA, 969 (63%) were women
- Women and men were comparable in age, BEC, and body mass index (Table 2)
- Mean IgE concentrations were lower for women (514 IU/mL) than men (771 IU/mL) (Table 2)
- The ratio of prebronchodilator forced expiratory volume in 1 second/forced vital capacity (FEV₁/FVC) was numerically smaller for men compared with women (Table 2)

Table 2. Baseline Characteristics for Women and Men with Baseline Blood Eosinophil Counts ≥ 300 cells/ μ L Enrolled in SIROCCO and CALIMA

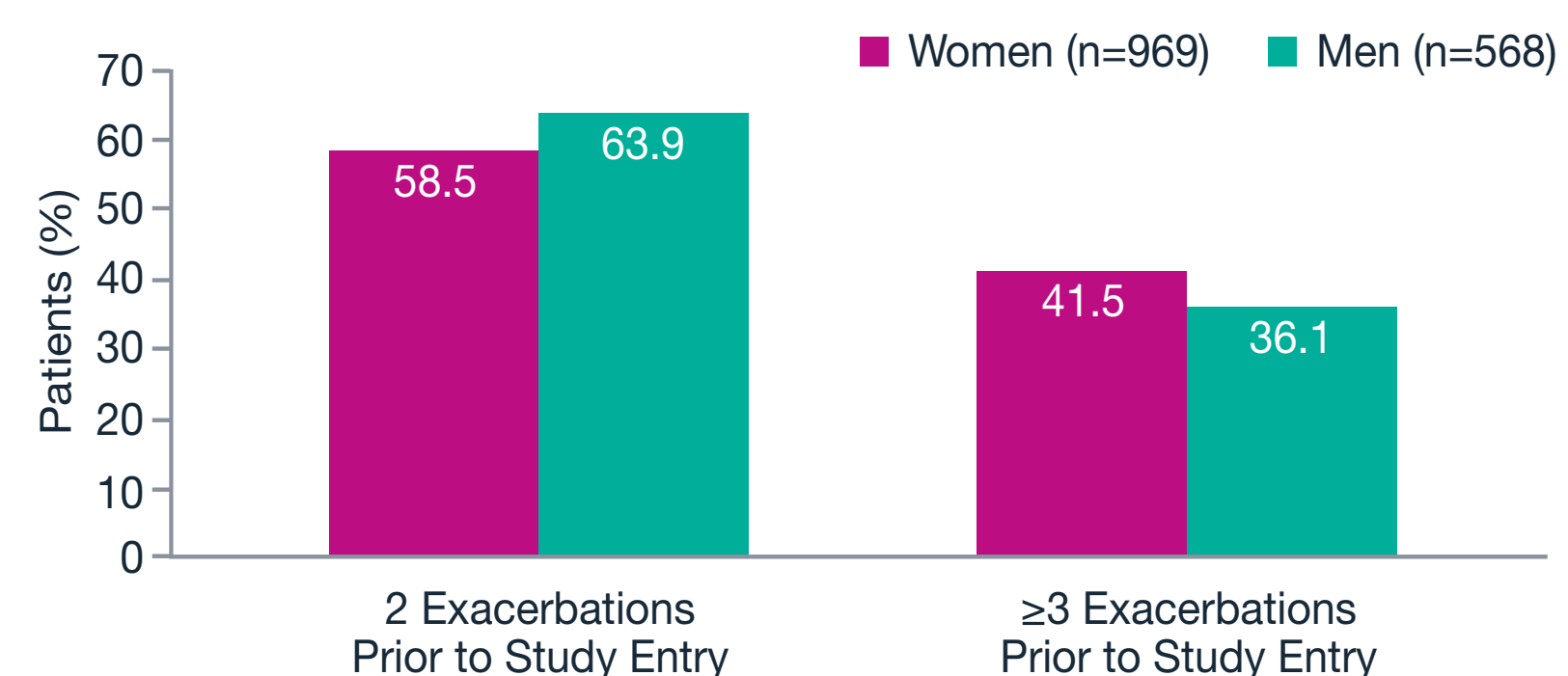
Baseline characteristic	Women (n=969)	Men (n=568)
Age [years], mean (SD)	49.4 (13.1)	48.1 (14.9)
BEC [cells/ μ L], median (Q1, Q3)	470 (330, 730)	480 (350, 710)
BMI [kg/m ²], mean (SD)	29.2 (7.4)	27.7 (5.0)
IgE concentration [IU/mL], mean	514 (1080.2)	771 (2491.1)
Prebronchodilator FEV ₁ [% PN], mean (SD)	57.4 (14.0)	56.5 (14.7)
Prebronchodilator FVC [% PN], mean (SD)	75.4 (15.2)	77.5 (15.4)
Prebronchodilator FEV ₁ /FVC [%], mean (SD)	62.0 (12.1)	58.5 (12.5)

BEC=Blood eosinophil counts; BMI=body mass index; FEV₁=forced expiratory volume in 1 second; FVC=forced vital capacity; IgE=immunoglobulin E; PN=predicted normal; Q=quartile; SD=standard deviation.

- Asthma reversibility was 26.4% for women and 25.0% for men
- Baseline exacerbation rates for women and men were 2.9 and 2.8, respectively

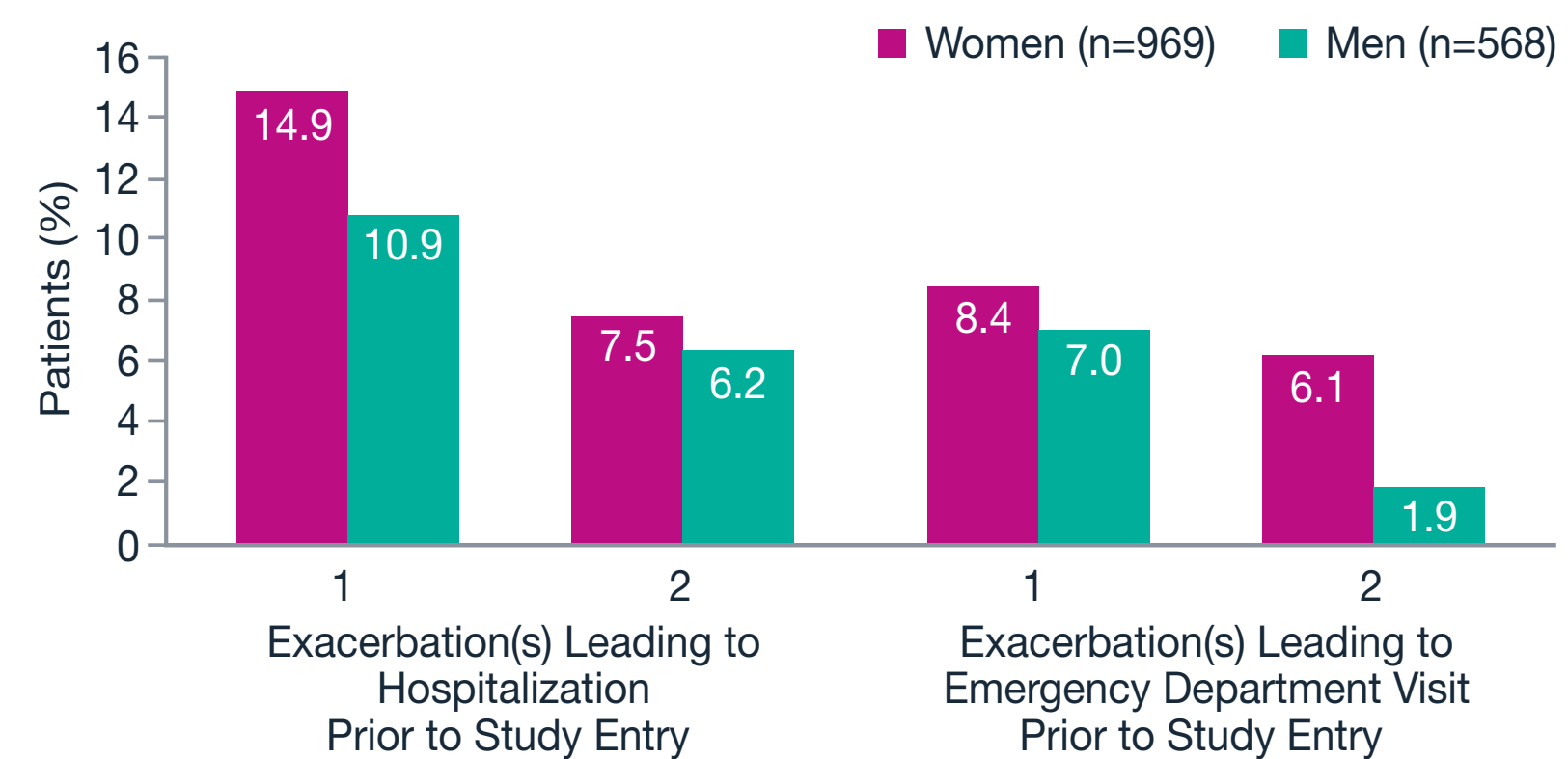
- More women than men experienced ≥ 3 exacerbations prior to study entry (41.5% vs. 36.1%, respectively) (Figure 1)

Figure 1. Asthma Exacerbations Prior to Study Entry for Women and Men with Baseline Blood Eosinophil Counts ≥ 300 cells/ μ L Enrolled in SIROCCO and CALIMA



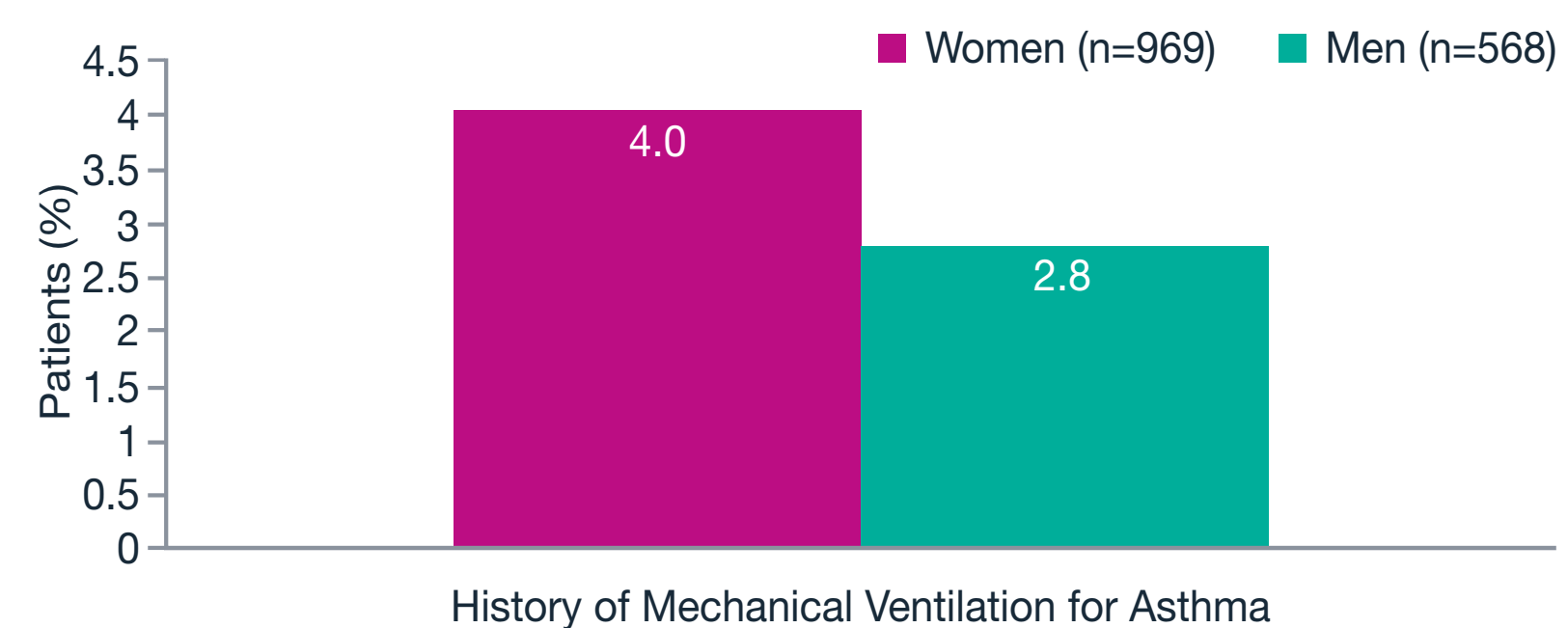
- Prior to study entry, more women than men had exacerbations leading to hospitalization or emergency department visits (Figure 2)

Figure 2. Asthma Exacerbations Leading to Hospitalization or Emergency Department Visit Prior to Study Entry for Women and Men with Baseline Blood Eosinophil Counts ≥ 300 cells/ μ L Enrolled in SIROCCO and CALIMA



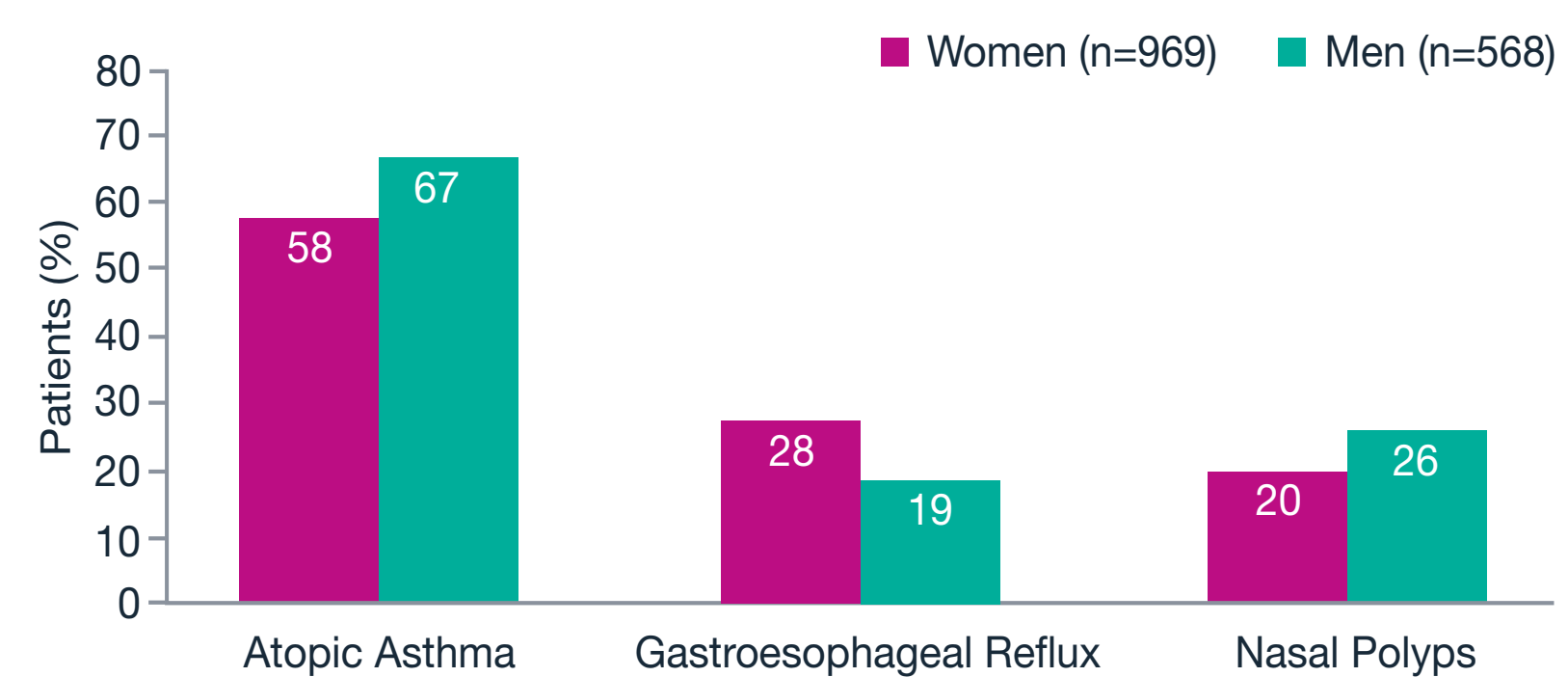
- At baseline, more women than men (4.0% vs. 2.8%) reported a history of mechanical ventilation for asthma (Figure 3)

Figure 3. History of Mechanical Ventilation for Asthma for Women and Men with Baseline Blood Eosinophil Counts ≥ 300 cells/ μ L Enrolled in SIROCCO and CALIMA



- A greater percentage of women had gastroesophageal reflux, and a lesser percentage of women had atopic asthma and nasal polyps at baseline (Figure 4)

Figure 4. Disease Characteristics at Baseline for Women and Men with Baseline Blood Eosinophil Counts ≥ 300 cells/ μ L Enrolled in SIROCCO and CALIMA



Conclusions

- As previously shown, baseline characteristics were similar between women and men enrolled in the SIROCCO and CALIMA Phase III trials with baseline BEC ≥ 300 cells/ μ L^{23,24,27,30}
- Benralizumab has demonstrated similar clinical benefit for both women and men with severe, eosinophilic asthma, with similar reductions in exacerbation risk and improvements in lung function regardless of IgE concentrations^{23,24,27,30}
- Women had more severe baseline disease (e.g., increased number of exacerbations, more exacerbations leading to hospitalization and emergency department visits), and were more likely to have had a history of mechanical ventilation for asthma despite being less likely to have had atopic asthma and having lesser IgE concentrations, suggesting that IgE is a poor predictor of disease severity
- These data support differences in severe eosinophilic asthma between women and men that should be factored into their clinical care

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