

More than a decade follow-up in patients with severe or difficult-to-treat asthma: The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) II

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Background: The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR I) study demonstrated high morbidity in patients with severe or difficult-to-treat asthma despite standard-of-care treatment.

Objective: We sought to determine the long-term natural history of disease and outcomes in patients in TENOR I after more than a decade.

Methods: TENOR I was a multicenter observational study (2001-2004) of 4756 patients with severe or difficult-to-treat asthma. TENOR II was a follow-up study of TENOR I patients using a single cross-sectional visit in 2013/2014. Overall, the sites participating in TENOR II originally enrolled 1230 patients in TENOR I. Clinical and patient-reported outcomes were assessed, including very poorly controlled asthma based on National Heart, Lung, and Blood Institute guidelines.

Results: A total of 341 (27.7%) patients were enrolled in TENOR II and were representative of the TENOR I cohort. The most frequent comorbidities were rhinitis (84.0%), sinusitis (47.8%), and gastroesophageal reflux disease (46.3%). Mean percent predicted prebronchodilator and postbronchodilator FEV₁ were 72.7% (SD, 21.4%) and 78.2% (SD, 20.7%), respectively. A total of 231 (72.9%) of 317 patients had positive test responses to 1 or more allergen-specific IgEs. The mean blood eosinophil count was 200/ μ L (SD, 144/ μ L). Eighty-eight (25.8%) patients experienced an asthma exacerbation in the prior 3 months requiring hospital attention, oral corticosteroids,

or both. More than half (197/339 [58.1%]) had very poorly controlled asthma. Medication use suggested undertreatment. **Conclusion:** TENOR II provides longitudinal data to characterize disease progression, heterogeneity, and severity in patients with severe or difficult-to-treat asthma. Findings show continued morbidity, including a high degree of comorbid conditions, allergic sensitization, exacerbations, and very poorly controlled asthma, including reduced lung function. (*J Allergy Clin Immunol* 2017;■■■■:■■■-■■■.)

Key words: Asthma, severe, difficult-to-treat, control, long-term, observational study, follow-up, the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens, exacerbations

Severe or difficult-to-treat asthma accounts for a large proportion of the morbidity, mortality, and health care costs associated with asthma.¹⁻⁵ There remains a significant unmet need in these patients in part because of resistance to asthma therapies.⁶ Several studies are investigating the characteristics and mechanisms involved in severe asthma to guide treatment advances.⁶⁻¹¹ Such studies have enabled a better recognition of severe asthma as a heterogeneous condition comprising multiple phenotypes.^{1,6-13} Indeed, differing pathologic processes or endotypes might be involved with each phenotype, suggesting a need for specific individualized therapy.⁷

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Abbreviations used

AAAQ:	Adult Asthma Adherence Questionnaire
ATAQ:	Asthma Therapy Assessment Questionnaire
ATS:	American Thoracic Society
ED:	Emergency department
FENO:	Fraction of exhaled nitric oxide
FVC:	Forced vital capacity
GERD:	Gastroesophageal reflux disease
MiniAQLQ:	Mini Asthma Quality of Life Questionnaire
NHLBI:	National Heart, Lung, and Blood Institute
PRO:	Patient-reported outcome
TENOR:	The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens
WPAI-Asthma:	Work Productivity and Activity Impairment Questionnaire for Asthma

Advances have also been made in understanding the biology and clinical features of severe asthma. For example, patients with severe asthma often show persistent airflow obstruction, higher comorbidity, and higher sputum and blood eosinophil counts than patients with less severe asthma, despite appropriate treatment.^{11,14} Additionally, very poorly controlled asthma has been linked to increased risk of future exacerbations.¹⁵

The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) I study is the largest cohort study of patients (770 children, 497 adolescents, and 3489 adults) with severe or difficult-to-treat asthma.⁸ It examined the natural history and unmet needs of patients by evaluating burden of illness, quality of life, asthma control and exacerbations, IgE and allergen sensitization, genetic markers, and special populations, such as the elderly and aspirin-sensitive patients.¹⁶ It highlighted a lack of disease control in patients with severe or difficult-to-treat asthma resulting in high levels of health care use, including hospitalizations, emergency department (ED) visits, intubations, and systemic corticosteroid bursts, despite standard-of-care asthma treatments.¹⁶

TENOR II is a follow-up observational study designed to describe the characteristics, long-term outcomes, and natural history of patients with severe or difficult-to-treat asthma more than 10 years after enrollment in the TENOR I study. This article presents the TENOR II study methods, baseline demographics, and clinical characteristics of patients enrolled in this follow-up study.

METHODS

TENOR I study design and population

The design of TENOR I has been presented elsewhere.⁸ It was a 3-year (2001-2004), prospective, multicenter, observational study that enrolled 4756 patients in the United States. Patients were aged 6 years or older with physician-assessed severe or difficult-to-treat asthma who had received treatment for 1 or more years with either high health care use (≥ 2 unscheduled asthma care visits or ≥ 2 oral corticosteroid bursts) or high medication use (requiring ≥ 3 asthma controller medications, long-term daily high doses of inhaled corticosteroids, or use of ≥ 5 mg/d oral prednisone) in the prior 12 months. Exclusion criteria included heavy smoking (≥ 30 pack-years), cystic fibrosis, severe cardiovascular disease, cancer, severe psychiatric disorder, or significant systemic disease.

TENOR II study design and population

TENOR II was a multicenter observational study with a follow-up assessment of patients with severe or difficult-to-treat asthma from the original TENOR I study. It was conducted between December 17, 2013, and December 19, 2014, and comprised a single study visit. All TENOR I sites were invited to participate. Recruitment efforts included e-mail/personal contact from TENOR Advisory Board members, Medical Directors, and Medical Science Liaisons from Genentech (South San Francisco, Calif) and Novartis Pharmaceuticals (East Hanover, NJ). Fifty-nine of the 283 sites participating in TENOR I enrolled patients in TENOR II. As in TENOR I, TENOR II was noninterventional, with patients receiving standard-of-care treatment for their asthma as prescribed by their clinician.

The TENOR II study protocol was approved by an institutional review board for each center. All participants provided written informed consent to participate.

Calculation of sample size

Sample size calculations were based on the ability to address the primary objective of TENOR II, namely to estimate the proportion of patients with very poorly controlled asthma based on the National Heart, Lung, and Blood Institute (NHLBI) impairment domain with a reasonable degree of precision. For sample sizes ranging from 400 to 600 and estimated proportions of very poorly controlled asthma of 0.3 and 0.5, the projected widths of the 95% CIs for the true proportion ranged from 7.3% (for the largest sample size and lowest estimated proportion) to 9.8% (for the smallest sample size and highest estimated proportion). Given the actual sample size of 341, the precision of the estimated proportions of very poorly controlled asthma of 0.3 and 0.5 was just slightly lower, with projected 95% CI widths for the true proportion of 9.7% and 10.6%, respectively (see the Methods section and [Tables E1](#) and [E2](#) in this article's Online Repository at www.jacionline.org).

Data collection

Data in TENOR II were collected by using electronic case report forms submitted to a Web-based data collection system. Variables in TENOR II were collected in the same manner as for TENOR I and included demographics, personal and family asthma history, comorbid conditions, current and prior (in the past 6 months) asthma-related medication use, self-reported health care use in the prior 3 and 12 months, self-reported asthma triggers, self-reported residential and occupational exposures, and targeted adverse events.⁸ New variables collected in TENOR II included additional comorbid conditions; use of additional allergy and asthma medications, including approved and experimental biologics; sun exposure; and additional asthma triggers (air pollution and nontobacco smoke) (see [Tables E3](#) and [E4](#) in this article's Online Repository at www.jacionline.org).

Patient-reported outcomes

Patient-reported outcomes (PROs) included the same validated instruments used in TENOR I, including the Asthma Therapy Assessment Questionnaire (ATAQ) to assess symptoms/control,^{17,18} the Work Productivity and Activity Impairment Questionnaire for Asthma (WPAI-Asthma) for work and productivity loss and activity impairment,^{19,20} and the Juniper Mini Asthma Quality of Life Questionnaire (MiniAQLQ) to evaluate asthma-related quality of life.²¹ In TENOR II a PRO instrument was added to assess medication adherence: the Adult Asthma Adherence Questionnaire (AAAQ; see the [Methods](#) section in this article's Online Repository).²²

Laboratory assessments

Laboratory tests included measurement of total serum IgE levels (also collected in TENOR I) plus 25-OH vitamin D levels, eosinophil counts, basophil counts, and specific IgE levels by using ImmunoCAP (Phadia, Uppsala, Sweden), RAST, and HYCOR methodologies. These were assessed

by using blood samples collected at the study visit, which were sent to Novartis or a designated central laboratory for analysis. Atopy was defined as having at least 1 positive specific IgE reading based on a threshold of 0.35 kU/L.²³

Spirometry

Patients also had spirometry and fraction of exhaled nitric oxide (FENO) measurements during the study visit. FENO assessments were performed at sites where a calibrated portable device (NIOX MINO; Aerocrine AB, Solna, Sweden) was available. Measurement of FENO values was performed according to American Thoracic Society (ATS)/European Respiratory Society guidelines.²⁴ At least 2 measurements were taken, and a mean value was recorded. Lung function was measured using prebronchodilator and postbronchodilator FEV₁ and forced vital capacity (FVC) with local spirometry.²⁵ Spirometry was performed using ATS/European Respiratory Society standardization before and after administration of 360 µg of albuterol.

Outcome measures

Patients were categorized based on the level of asthma control (very poorly controlled, not well controlled, and well controlled) according to the impairment domain of the NHLBI/National Asthma Education and Prevention Program Expert Panel Review-3 guidelines.²⁶ Variables included symptoms, nighttime awakenings, interference with normal activity, ATAQ scores measuring asthma symptoms and control, short-acting β_2 -agonist use for symptom control, and lung function, as determined by measurement of FEV₁ or peak flow.

Other outcome measures included asthma exacerbations in the 3 and 12 months before TENOR II enrollment. An exacerbation was defined as an asthma-related overnight hospitalization or asthma-related visit to the ED or as any oral corticosteroid treatment. Asthma exacerbations were also graded according to severity in descending order: (1) asthma-related overnight hospitalization, (2) asthma-related ED visit, and (3) oral corticosteroid treatment. The ATS definition of severe exacerbation (ie, a hospitalization or ED visit caused by asthma that required systemic corticosteroids) was also used.²⁷

Other outcome measures included the number of days missed from work because of asthma in the 7 days before the study evaluation assessed using WPAI-Asthma, and asthma-related quality of life assessed using the Mini-AQLQ. Lower scores on the MiniAQLQ indicate poorer asthma-related quality of life (7 = no impairment, 1 = severe impairment; see the Methods section in this article's Online Repository for full details).

Statistical analyses

Descriptive statistics were generated for demographic and baseline characteristics for TENOR I and TENOR II. Mean and SD, median and interquartile range, and minimum and maximum values were reported for all biomarkers. For total IgE levels, the geometric mean and its associated 95% CI were reported.²⁸

Comparisons of demographic characteristics were made between the TENOR II sample (n = 341) and TENOR I patients at sites participating in TENOR II (n = 1230) to assess the generalizability of the TENOR II sample to the wider patient population at enrolling sites. A comparison was also made between the TENOR II sample (n = 341) and the full TENOR I cohort (n = 4756) to confirm generalizability with the original TENOR I patient population.

Because the TENOR II patient population involved a smaller proportion of the TENOR I cohort, there was a risk of biased estimates. Data from the original TENOR I baseline were used to protect against these biases by modeling predictors of enrollment in the 10-year follow-up adjusted for these factors using a logistic regression model (see the Methods section and Fig E1 in this article's Online Repository at www.jacionline.org for further details on how weighting was applied to adjust for possible selection bias).

RESULTS

Demographic and clinical characteristics

The 59 centers that enrolled 341 patients in TENOR II had previously enrolled a total of 1230 patients in TENOR I (see Fig E2 in this article's Online Repository at www.jacionline.org). At the time of enrollment in TENOR I, 308 of the TENOR II patients had been adults (aged ≥ 18 years), 15 had been adolescents (12-17 years), and 18 had been children (6-11 years).

The mean age of the 341 patients enrolled in TENOR II was 57.8 years (SD, 16.3 years), and the mean body mass index was 30.6 kg/m² (SD, 7.2 kg/m²; Tables I and II).^{29,30} The majority of patients were female (65.4%) and white (80.1%). A high percentage of patients (24.6%) were current or former smokers, with a mean history of 14.4 (SD, 18.0) pack years. Mean percent predicted prebronchodilator and postbronchodilator FEV₁ values were 72.7% (SD, 21.5%) and 78.2% (SD, 20.7%), respectively, and z scores were -1.7 (SD, 1.4) and -1.4 (SD, 1.3), respectively. The postbronchodilator FEV₁/FVC ratio was less than 0.7 in 140/328 patients (42.7%). Most patients (78.0%) were being treated by an allergist, and nearly three quarters (72.9%) were atopic.

Sensitivity analysis

Preliminary comparisons suggested TENOR II patients were generally representative of the TENOR I cohort (see the Methods section in this article's Online Repository).

Comorbidities

A broad range of comorbidities were reported in TENOR II (Table III). The most common were allergic rhinitis (84.0%), sinusitis (47.8%), gastroesophageal reflux disease (GERD; 46.3%), and hypertension (42.5%). Increased/ease of bruisability, upper respiratory tract infection, food allergy, and cataracts were reported by approximately 30% to 34% of patients.

Biomarkers

The geometric mean total IgE level was 72.2 IU/mL (95% CI, 58.0-89.9 IU/mL; Table IV). Overall, about 60% of patients had total IgE levels of 30 to 700 IU/mL. Mean blood eosinophil and basophil counts were 200/ μ L (SD, 144/ μ L) and 53/ μ L (SD, 55/ μ L), respectively, and the mean FENO value was 29.1 ppb (SD, 28.8 ppb). Table E5 in this article's Online Repository at www.jacionline.org shows biomarker levels by asthma control category.

Current asthma medications

At the TENOR II study visit, 71.0% of patients were taking combined inhaled corticosteroids and long-acting β_2 -agonists, and 39.6% were taking a leukotriene modifier (Table V). Systemic corticosteroids and long-acting anticholinergic/muscarinic antagonists were each used by 11.2% of patients, and 11.8% were taking omalizumab.

Level of control

Based on the NHLBI asthma guidelines impairment domain, more than half (58.1%) of patients in the TENOR II cohort were classified as having very poorly controlled asthma, and 34.2%

TABLE I. Baseline demographics and clinical characteristics of TENOR I and TENOR II patients demonstrating generalizability of the TENOR II population*

	At time of TENOR II enrollment		At time of TENOR I enrollment		
	(A) TENOR II patients (n = 341)	(B) TENOR II patients at time of TENOR I enrollment (n = 341)	(C) TENOR I patients at sites participating in TENOR II (n = 1230)	(D) TENOR I patients at sites participating in TENOR II who did not enroll into TENOR II (n = 889)	(E) TENOR I patients (n = 4756) [§]
Age at enrollment (y), mean $\pm$ SD	57.8 $\pm$ 16.3	44.6 $\pm$ 16.3	42.9 $\pm$ 19.0	42.2 $\pm$ 19.9	38.9 $\pm$ 20.9
Sex, no. (%) [†]					
Female	223 (65.4)	221 (64.8)	782 (63.6)	561 (63.1)	2945 (62.2)
Male	118 (34.6)	120 (35.2)	448 (36.4)	328 (36.9)	1792 (37.8)
Race, no. (%)					
White	273 (80.1)	273 (80.1)	990 (80.6)	717 (80.8)	3555 (75.1)
Black	38 (11.1)	38 (11.1)	135 (11.0)	97 (10.9)	712 (15.0)
Hispanic	22 (6.5)	22 (6.5)	73 (5.9)	51 (5.7)	303 (6.4)
Asian/Pacific Islander	4 (1.2)	4 (1.2)	18 (1.5)	14 (1.6)	72 (1.5)
American Indian/Alaskan Native	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	19 (0.4)
Other	4 (1.2)	4 (1.2)	11 (0.9)	7 (0.8)	72 (1.5)
Site specialty, no. (%)					
Pulmonologist	71 (22.0)	71 (22.0)	261 (22.5)	190 (22.7)	1656 (36.2)
Allergist	251 (78.0)	251 (78.0)	897 (77.5)	646 (77.3)	2922 (63.8)
FEV ₁ , mean $\pm$ SD					
Prebronchodilator [‡] (% predicted)	72.7 $\pm$ 21.4	72.8 $\pm$ 21.4	73.3 $\pm$ 23.0	73.5 $\pm$ 23.6	75.8 $\pm$ 22.5
Postbronchodilator (% predicted) [‡]	78.2 $\pm$ 20.7	77.9 $\pm$ 21.1	78.5 $\pm$ 21.8	78.7 $\pm$ 22.1	81.2 $\pm$ 22.1
Prebronchodilator (% predicted) [§]	73.3 $\pm$ 21.4	73.5 $\pm$ 21.2	73.9 $\pm$ 22.5	74.0 $\pm$ 23.0	76.3 $\pm$ 22.1
Postbronchodilator (% predicted) [§]	78.9 $\pm$ 20.6	78.7 $\pm$ 20.9	79.2 $\pm$ 21.5	79.3 $\pm$ 21.8	81.7 $\pm$ 21.6
Prebronchodilator (z score) [§]	-1.7 $\pm$ 1.4	-1.9 $\pm$ 1.5	-1.8 $\pm$ 1.5	-1.8 $\pm$ 1.6	-1.7 $\pm$ 1.6
Postbronchodilator (z score) [§]	-1.4 $\pm$ 1.3	-1.5 $\pm$ 1.5	-1.5 $\pm$ 1.5	-1.4 $\pm$ 1.5	-1.3 $\pm$ 1.5
FEV ₁ median (IQR)					
Prebronchodilator (% predicted) [‡]	72.8 (27.2)	74.4 (29.3)	73.8 (30.9)	73.8 (31.7)	76.6 (30.8)
Postbronchodilator (% predicted) [‡]	78.1 (27.1)	78.7 (26.1)	79.6 (29.4)	79.7 (30.3)	82.0 (28.8)
Prebronchodilator (% predicted) [§]	73.8 (28.1)	75.9 (29.5)	74.8 (31.2)	74.4 (31.9)	77.2 (30.8)
Postbronchodilator (% predicted) [§]	78.9 (26.1)	80.8 (28.2)	80.8 (29.1)	80.9 (29.9)	82.6 (29.1)
Prebronchodilator (z score) [§]	-1.7 (1.8)	-1.8 (2.1)	-1.8 (2.2)	-1.9 (2.2)	-1.7 (2.1)
Postbronchodilator (z score) [§]	-1.4 (1.7)	-1.4 (2.0)	-1.4 (2.0)	-1.4 (2.1)	-1.3 (2.1)

IQR, Interquartile range.

*A total of 283 sites participated in TENOR I, comprising a total of 4756 participants (column E). Fifty-nine of these sites also participated in TENOR II. These 59 sites had previously recruited 1230 subjects to TENOR I (column C). Of these 1230 subjects, 341 went on to also participate in TENOR II (data shown in column A at the time of TENOR II and column B at the time of TENOR I). Column D displays data for the 889 remaining subjects (ie, 1230 minus 341 subjects) who did not join TENOR II.

[†]Two patients were identified as male at the time of TENOR I but were identified as female in TENOR II.

[‡]Hankinson estimates of percent predicted prebronchodilator and postbronchodilator FEV₁ were derived from the National Health and Nutrition Examination Survey III reference equations.²⁹

[§]Global Lung Function Initiative estimates of percent predicted prebronchodilator and postbronchodilator FEV₁ and z scores were derived from the Global Lung Function Initiative reference equations.³⁰

were classified as having not well-controlled asthma. Only a small proportion (7.7%) of patients had well-controlled asthma.

Asthma exacerbations

Eighty-eight (25.8%) of 341 patients reported an asthma exacerbation in the 3 months before the TENOR II study visit. Of these patients with recent exacerbations, 19 (21.6%) reported an ED visit or hospitalization, and 79 (89.8%) represented exacerbations that required oral corticosteroid therapy. Nearly 15% of patients had experienced a severe exacerbation based on the ATS definition during this period.

During the 12 months before TENOR II, 164 (48.2%) of 341 patients experienced an exacerbation. Of these, 44 (26.8%) had an ED visit or hospital stay, 158 (96.3%) required a corticosteroid burst, and 35 (21.3%) reported a severe exacerbation.

PROs

The mean overall MiniAQLQ score for the TENOR II cohort was 4.2 (SD, 1.3), with the lowest score in the environmental stimuli domain (ie, 3.7 [SD, 1.7]), followed by symptoms

(4.3 [SD, 1.3]), emotional function (4.3 [SD, 1.7]), and activity limitation (4.6 [SD, 1.5]). The overall mean percentage activity impairment, as measured by using WPAI-Asthma, reported by patients was 21.0% (SD, 25.9%). The percentage of work time missed was 6.3% (SD, 63.5%), and the percentage loss in productivity while at work was 10.6% (SD, 17.8%). The percentage of overall work impairment was 13.3% (SD, 34.8%; see Table E6 in this article's Online Repository at www.jacionline.org).

Based on the ATAQ score, 42.5% of patients reported no barriers to asthma control, 22.6% reported 1 barrier, 22.3% reported 2 barriers, 34.9% reported 2 or more barriers, and 12.6% reported 3 or more barriers. The most common barrier to treatment adherence based on the AAAQ was the patient not perceiving that his or her condition warranted preventative treatment (45.5% of patients). Costs and side effects were also common barriers to adherence (reported by 37.4% and 32.8% of patients, respectively). Overall, 28.1% of patients reported instances in which they forgot to take their treatment, and 9.4% did not follow the medication plan.

TABLE II. Additional clinical characteristics of the TENOR II cohort

	TENOR II patients (n = 341)
BMI (kg/m ²), mean ± SD	30.6 ± 7.2
Education, no. (%)	
High school or less	74 (21.9)
Any college or more	264 (78.1)
Employment status, no. (%)	
Working	173 (50.7)
Not working	168 (49.3)
Smoking history, no. (%) [*]	
Never smoked	255 (75.4)
Past smokers	74 (21.9)
Currently smoke	9 (2.7)
Smoking (pack years)	
Mean ± SD	14.4 ± 18.0
Median (IQR)	7.5 (18.2)
Any positive specific IgE (n = 317), no. (%) [†]	231 (72.9)

BMI, Body mass index; IQR, interquartile range.

^{*}From 338 patients reporting smoking history.[†]Defined as having at least 1 positive specific IgE reading using a threshold of 0.35 kU/L.

DISCUSSION

The economic costs of asthma are known to be predominantly caused by uncontrolled disease, and control-based asthma management has been the foundation of asthma guidelines for several years, as assessed by domains of impairment and future risk of exacerbations.^{1,26,31} The TENOR II study is a long-term follow-up study of a subgroup of patients with severe or difficult-to-treat asthma more than a decade after enrollment in TENOR I. The objective of the study was to better understand the long-term outcomes and natural history of severe or difficult-to-treat asthma by characterizing disease burden.⁸ Comorbid conditions were common in this cohort, with allergic rhinitis, sinusitis, GERD, and hypertension being present in more than 40% of patients. Nearly three quarters of patients were atopic, and 60% had an IgE level of 30 to 700 IU/mL. Prebronchodilator and postbronchodilator percent predicted FEV₁ had changed little between TENOR studies. About 70% of patients were taking inhaled corticosteroids, long-acting β_2 -agonists, or both, and only about 12% were taking omalizumab. More than half of the patients in the TENOR II cohort had very poorly controlled asthma, and approximately a quarter reported an asthma exacerbation in the 3 months before the study visit. PRO data demonstrated low quality of life scores in all domains, and 47.5% of patients reported at least 2 barriers to asthma control. Barriers to treatment adherence were common.

There remains substantial unmet need in patients in the TENOR II study, despite standard-of-care therapy. Evaluations of medication use in TENOR II showed that 87.0% of patients required short-acting β_2 -agonists, and 71.0% to 84.0% used inhaled corticosteroids, long-acting β_2 -agonists, or both. In contrast, only 11.8% had been prescribed omalizumab and 11.2% were using systemic corticosteroids, despite the high rate of exacerbations, high level of atopy, increased IgE levels, and high percentage of patients with very poorly controlled asthma. The TENOR II study findings suggest undertreatment in this cohort of patients with severe or difficult-to-treat asthma, which suggests that clinicians might not be adhering to asthma guidelines and adjusting therapy as appropriate.^{32,33}

TABLE III. Comorbidities reported in TENOR II (n = 341)

Comorbidity	No. (%)
Allergic rhinitis [†]	285 (84.1)
Acute or chronic sinusitis [*]	163 (47.8)
GERD [*]	158 (46.3)
High blood pressure [*]	145 (42.5)
Increased/ease of bruisability [*]	117 (34.3)
Upper respiratory tract infection [*]	109 (32.0)
Food allergy [*]	104 (30.5)
Cataracts	102 (29.9)
Insomnia [*]	84 (24.6)
Obesity [*]	75 (22.0)
Nasal polyps [*]	73 (21.4)
Aspirin sensitivity	66 (19.4)
Obstructive sleep apnea [*]	65 (19.1)
History of nasal polypectomies [*]	63 (18.5)
Osteoporosis and osteoporotic fractures	54 (15.8)
Urticaria/hives	53 (15.5)
Type 2 diabetes	53 (15.5)
Rash	48 (14.1)
Chronic obstructive pulmonary disease	43 (12.6)
Chronic bronchitis	41 (12.0)
Other heart disease [*]	36 (10.6)
History of malignancy (including lymphoma) [*]	33 (9.7)
Anaphylaxis	28 (8.2)
Rheumatoid arthritis	25 (7.3)
Other allergic reactions	21 (6.2)
Inflammatory bowel disease [*]	21 (6.2)
Coronary artery disease [*]	19 (5.6)
Glaucoma [*]	18 (5.3)
Vocal cord dysfunction	18 (5.3)
Acute or chronic urticarial/angioedema [*]	17 (5.0)
Restrictive lung disease [*]	14 (4.1)
History of bariatric surgeries [*]	9 (2.6)
Chronic idiopathic urticaria [*]	9 (2.6)
Congestive heart failure [*]	8 (2.3)
Opportunistic infection [*]	7 (2.1)
Thrombocytopenia	6 (1.8)
Sjögren syndrome	3 (0.9)
Type 1 diabetes	2 (0.6)
Parasitic infection	2 (0.6)
Multiple sclerosis	1 (0.3)
Eosinophilic esophagitis [*]	1 (0.3)
Erythema multiforme	1 (0.3)
Other	88 (25.8)

Note: Patients might have had multiple comorbidities.

^{*}Comorbidities measured only in TENOR II.[†]Allergic rhinitis incidence was obtained from participants' responses to medical history questions on the personal medical history form ("Have you ever had a problem with sneezing or a runny/blocked nose when you did not have a cold?") rather than being collected through comorbidity reporting (n = 339).

The observation of consistently reduced lung function in TENOR II patients suggests an irreversible component in severe or difficult-to-treat asthma. Indeed, the lack of change in FEV₁ over the follow-up period might indicate that lung remodeling and irreversible lung disease had already occurred if these patients remained poorly controlled despite treatment. Long-term serial follow-up would be needed to confirm this observation. This phenomenon has been observed in other severe asthma cohorts and longitudinal studies of childhood asthma, with baseline lung function also affecting longitudinal outcomes.³⁴⁻³⁷ It is also possible that individual variation in lung function might account for the minimal change in FEV₁ over time because some patients might have shown an increase in FEV₁ in response to treatment,

TABLE IV. Baseline biomarker values

Biomarker	Value
Total IgE (IU/mL) (n = 315)	
Geometric mean (95% CI)	72.2 (58.0-89.9)
Median (interquartile range)	77.2 (232)
Minimum-maximum	0-9672.8
<30 (%)	29.8
≥30 to <700 (%)	60.3
>700 (%)	9.8
Eosinophils (μL [n = 312])	
Mean ± SD	200 ± 144
Median (interquartile range)	200 (200)
Minimum-maximum	0-800
<150 (%)	44.6
150 to <300 (%)	29.5
≥300 (%)	26.0
Basophils (μL [n = 312])	
Mean ± SD	53 ± 55
Median (interquartile range)	100 (100)
Minimum-maximum	0-300
FeNO (ppb [n = 174])	
Mean ± SD	29.1 ± 28.8
Median (interquartile range)	21.5 (20)
Min-maximum	5.0-272.5
<25 (%)	59.2
25 to <50 (%)	30.5
≥50 (%)	10.3

whereas others showed a decrease because of progression despite treatment, which might have contributed to an apparent flat curve. The lung function measures in TENOR II represented values at 1 cross-sectional study visit. Patients should be followed carefully over time with multiple measures of spirometry to follow their lung function trajectory. The pattern of FEV₁ change can also be linked to the variable effects of genetic influences.³⁸

Consistently reduced lung function raises questions about the presence of asthma/chronic obstructive pulmonary disease overlap syndrome in this population and the need to examine treatment strategies.³⁹ The high prevalence of current/former smoking history in the TENOR II cohort could also affect the presence of asthma/chronic obstructive pulmonary disease overlap syndrome. Further analysis of lung function decrease over the long-term and maximal attained lung function in early adulthood in former smokers versus nonsmokers might be important in further understanding the role of tobacco exposure.^{35,40} Exacerbations can also be implicated in continued decrease of lung function because studies have linked severe asthma exacerbations with progression of irreversible airflow limitation.^{41,42} Aging and use of systemic corticosteroids might contribute to FVC decrease.^{42,43}

The comorbidity burden was high in TENOR II, with most patients reporting at least 1 condition in addition to their asthma. Clinicians should be aware of the interaction of these comorbidities with asthma, as well as their effect on asthma outcomes. Comorbidities need to be addressed if asthma symptoms remain uncontrolled.^{44,45} Rhinitis and sinusitis are common comorbidities with asthma and might share similar pathophysiologic mechanisms.^{44,45} GERD is also commonly seen in patients with asthma and, although a side effect of asthma management, is linked with poor asthma control.⁴⁶ Obesity increases the risk of asthma exacerbations, with even a 5-pound weight gain having an effect.^{47,48}

Obesity can also play an important role in reducing responses to asthma therapy, with studies suggesting that obese patients represent a phenotype in whom symptoms are particularly hard to control.^{44,49,50} Body weight had increased over the more than 10 years since TENOR I, with mean body mass index increasing from 28.3 kg/m² (within the overweight range) in the original TENOR I study to 30.6 kg/m² (classified as obese) in TENOR II. This finding suggests poor weight management among patients during longitudinal follow-up, despite its effect on asthma control, asthma exacerbations, and other comorbidities.⁴⁷ Food allergy was self-reported as a common comorbidity in the TENOR II cohort, and the previously discovered link between aspirin sensitivity and severe asthma remained apparent.⁵¹

The AAAQ instrument, a new validated adherence measure used in TENOR II, captured barriers to medication adherence. The most common reason for not adhering to treatment was the patient considering his or her condition to be sufficiently mild so as to not require preventative treatment. This is noteworthy because it contrasts with the clinical assessment of severe or difficult-to-treat asthma. However, other studies have found that asthmatic patients underestimate the severity of their condition and overestimate how well their disease is controlled.^{52,53} These findings suggest a need to educate asthmatic patients about recognizing the true state of their disease and the importance of treatment. Costs and side effects of medications were also important barriers to adherence, and unintentional nonadherence was reported by the TENOR II cohort. Fear of long-term side effects from regular use of inhaled corticosteroids is a well-known barrier to asthma control.^{54,55} Addressing adherence issues could improve the level of disease control in these patients but remains a challenge for clinicians.⁵⁵

Limitations of this study include the self-reported nature of several variables, including comorbidities and health care use. Also, there was a potential opportunity for misclassification of information when using the recall period of 1 year before the study visit. Another limitation was collection of the short-acting β_2 -agonist use component of asthma control, which was frequently described by sites as "as-needed." These responses were queried to clarify the specific frequency of use to classify patients into an NHLBI category, but this was not always possible. Patients might have also been reporting the prescribed frequency of short-acting β_2 -agonist use rather than actual use. However, a sensitivity analysis that examined asthma control categories excluding short-acting β_2 -agonist use did not affect the classification of asthma control.

Sample size might also be a limitation. Although sensitivity analyses demonstrated the representativeness of the TENOR II to the TENOR I cohort, it is possible that underlying selection biases might exist in the TENOR II cohort.

Finally, although a measure of adherence was included using a validated tool,⁶ this was a general assessment at a single follow-up visit rather than a specific measure of adherence to each medication type over a prolonged period. This limited the analyses of the effect of adherence on outcomes. The inclusion of only 1 observation point in TENOR II is also a limitation.

In summary, TENOR II provided an opportunity to examine the 10-year longitudinal history of patients with severe or difficult-to-treat asthma in a real-world setting. Patients in TENOR II, who were evaluated at least a decade after TENOR I, were characterized with a persistent high rate of very poorly controlled asthma, which was characterized by multiple comorbidities, frequent asthma exacerbations, and barriers to adherence. Future analyses of TENOR II data will further explore the longitudinal aspects of

TABLE V. Current medications taken by patients in TENOR II (n = 331)

Class of medication	Overall, no. (%)	Asthma control category, no. (%)		
		Well controlled (n = 22)	Not well controlled (n = 111)	Very poorly controlled (n = 196)
Short-acting β_2 -agonists	288 (87.0)	9 (40.9)	93 (83.8)	184 (93.9)
Inhaled corticosteroids	278 (84.0)	14 (63.6)	91 (82.0)	171 (87.2)
Low dose	53 (20.2)	7 (50.0)	23 (27.1)	23 (14.3)
High dose	96 (36.6)	2 (14.3)	29 (34.1)	64 (39.8)
Long-acting β_2 -agonists	246 (74.3)	10 (45.5)	83 (74.8)	151 (77.0)
Combined inhaled corticosteroids/ long-acting β_2 -agonists	235 (71.0)	10 (45.5)	77 (69.4)	146 (74.5)
Leukotriene modifiers	131 (39.6)	3 (13.6)	39 (35.1)	89 (45.4)
Oral nonsedating antihistamines	121 (36.6)	9 (40.9)	47 (42.3)	65 (33.2)
Intranasal steroids	113 (34.1)	9 (40.9)	50 (45.0)	53 (27.0)
Omalizumab	39 (11.8)	2 (9.1)	16 (14.4)	21 (10.7)
Intranasal nonsteroid medications	38 (11.5)	2 (9.1)	15 (13.5)	21 (10.7)
Systemic corticosteroids	37 (11.2)	0 (0.0)	6 (5.4)	30 (15.3)
Long-acting anticholinergic/ muscarinic antagonists	37 (11.2)	2 (9.1)	7 (6.3)	27 (13.8)
Short-acting anticholinergics	35 (10.6)	1 (4.5)	13 (11.7)	21 (10.7)
Proton pump inhibitors	30 (9.1)	0 (0.0)	13 (11.7)	17 (8.7)
Methylxanthines	25 (7.6)	2 (9.1)	6 (5.4)	17 (8.7)
Diphenhydramine	18 (5.4)	0 (0.0)	3 (2.7)	15 (7.7)
Atopic dermatitis medications	10 (3.0)	0 (0.0)	7 (6.3)	2 (1.0)
Acute sinusitis antibiotics	6 (1.8)	0 (0.0)	0 (0.0)	6 (3.1)
Epinephrine	6 (1.8)	0 (0.0)	3 (2.7)	3 (1.5)
H ₂ antagonists	4 (1.2)	0 (0.0)	1 (0.9)	3 (1.5)
Cromolyn sodium	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Patients might have been taking multiple medications. Counts of inhaled corticosteroids and long-acting β_2 -agonists include medications reported in the combined inhaled corticosteroids and long-acting β_2 -agonists row. The combined group includes the following medications: budesonide/formoterol, mometasone/formoterol, and fluticasone/salmeterol.

patients with severe and difficult-to-treat asthma, predictors of persistently very poorly controlled asthma and exacerbations, and the influence of atopy on asthma-related outcomes.

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Key messages

- This longitudinal assessment of patients with severe or difficult-to-treat asthma more than a decade after the TENOR I study showed continued morbidity, including a high degree of comorbid conditions, allergic sensitization, asthma exacerbations, very poorly controlled asthma, and reduced lung function.
- The level of asthma control in patients with severe or difficult-to-treat asthma appears to have changed minimally over the long-term, despite standard-of-care therapy.
- Medication data in TENOR II suggest patients might be undertreated and might not have had their treatment stepped up by clinicians, as advised in asthma guidelines. TENOR II patients also reported several barriers to adherence.

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METHODS

Methodology of the sample size calculation

Sample size calculations were based on the ability to address the objective of the TENOR II study and estimate the proportion of patients with very poorly controlled asthma based on the NHLBI impairment domain with a reasonable degree of precision. The precision of the estimates at sample sizes ranging from 400 to 600 is described in Table E1 using the projected widths of the CIs. The precision of the estimated proportions using the actual sample size of 341 is described in Table E2.

If the TENOR cohort remained severe or difficult to treat, approximately 30% to 50% of patients would have had very poorly controlled asthma based on NHLBI asthma control categories. There was some loss of precision at 400 rather than 600 patients, but the SEs remained close to 2%. A 400-patient study represented only 10% of the TENOR I cohort, although it might have represented more than 20% of the patients from sites participating in the long-term follow-up study.

Sensitivity analysis

Preliminary comparisons of age, race, FEV₁, and site specialty among TENOR I and TENOR II patients suggested that TENOR II patients at participating sites (n = 341) were generally representative of the broader TENOR II study cohort at participating sites (n = 1230), of the subjects at participating sites who did not enroll in TENOR II (n = 889), and of the original full TENOR I cohort (n = 4756, Table I). The weighted and unweighted results of the TENOR II data for asthma control and asthma exacerbations were similar, further demonstrating the representativeness of the TENOR II data to the TENOR I data (see Fig E1).

Methodology of the PRO measures

The ATAQ measures 5 conceptual domains essential for optimal asthma management: control, symptoms, communication and knowledge gaps, behavior/attitude, and self-efficacy barriers. These domains have been shown to correlate with other measures of impairment, health care use, and quality of life.^{E1} Scores range between 0 and 4, with higher scores indicating greater barriers to asthma control.^{E2}

WPAI-Asthma assesses impairment in work, school, and daily activities. The instrument is composed of 9 items representing 3 domains: work impairment (4 items), school impairment (4 items), and activity impairment (1 item).^{E3,E4} Values for each domain range from 0% to 100%, with higher scores indicating greater impairment.

The Juniper MiniAQLQ has 15 questions and assesses asthma-related quality of life using an overall score, as well as 4 domains (symptoms, activities, emotions, and environment). Scores range between 0 and 6, with 6 representing the most favorable score.^{E5}

The AAAQ is comprised of 5 questions related to measures of medication adherence and asthma control that can be used clinically to identify patients at risk of nonadherence and the specific adherence barriers involved, including following “my medication plan,” forgetting to take medication, lack of need for treatment, side effects, and cost.^{E6}

Data weighting used to protect against biased estimates: Methodology and results

Inverse probability weighting was used on key variables to predict enrollment in TENOR II.^{E7,E8} Predicted probabilities (*P* values) were computed directly from the fitted logistic regression model, and inverse probabilities (1/*P* value) were subsequently computed. The average of the inverse probabilities was calculated across all TENOR I patients. Dividing the inverse probability by the average resulted in the inverse probability weighting for that outcome. This weighting approach applied greater weights for underrepresented groups and smaller weights for overrepresented groups in TENOR II. Weights reflected the inverse probability of being enrolled in TENOR II as a function of age, sex, race, prebronchodilator percent predicted FEV₁, ATAQ index score, and exacerbations (hospitalizations or ED visit) in the months before enrollment. These factors, selected based on prior TENOR I analyses, the asthma literature, and an external committee of clinical experts in asthma, were known to have direct associations with the primary outcome of interest: very poorly controlled asthma. In the event that other differences were observed between the TENOR I study population and TENOR II study population, these variables were to be considered variables of interest and not necessarily variables “of concern” that could have a direct effect on the outcome of interest. The determination of whether the weighted results differed from the unweighted results was based on review by the external committee of clinical experts. The unweighted results were preferentially reported to the extent that the results appeared reasonably similar. This weighting strategy allowed generalizability with the TENOR I cohort if TENOR II participants appeared to be demographically or clinically different from nonparticipants based on the TENOR I baseline data.

Similarities between weighted and unweighted results support the generalizability of the TENOR II cohort to the original TENOR I cohort (see Fig E1). Thus unweighted results can be reported in future analyses of TENOR II findings without affecting the clinical interpretation of the data.

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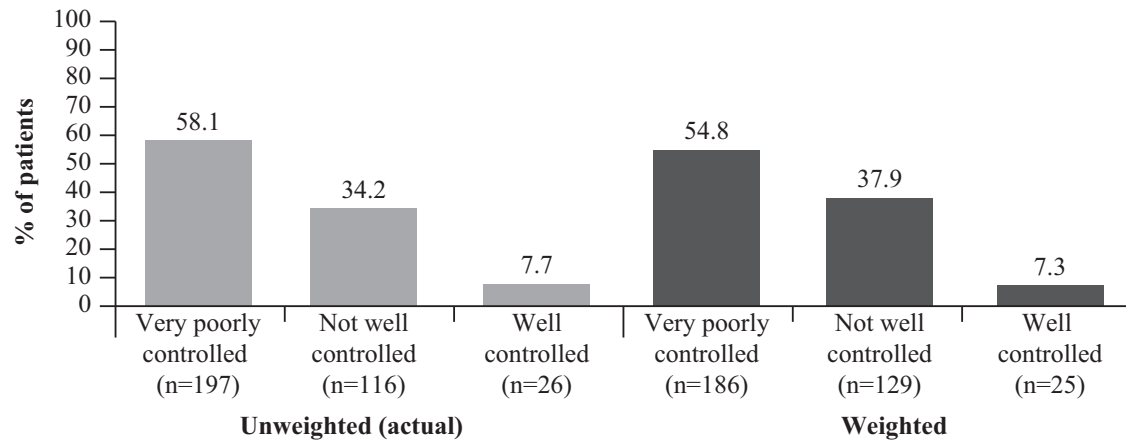


FIG E1. Comparison of asthma control using data weighting.

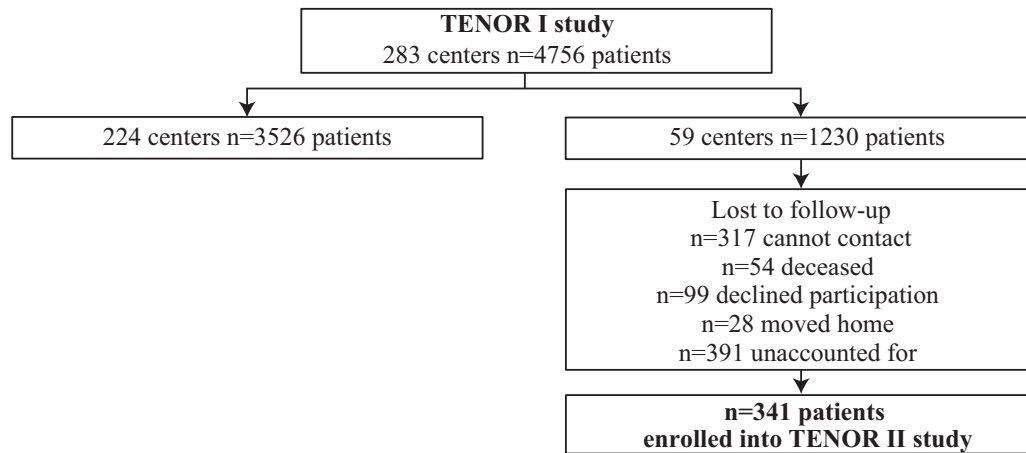


FIG E2. Patient inclusion and study center involvement in TENOR I and TENOR II.

TABLE E1. Estimates of very poorly controlled diagnosis
precision based on study size

Estimated proportion	Sample size	SE	SE × 1.96	CI width
0.3	400	2.3%	4.5%	9.0%
0.3	500	2.0%	4.0%	8.0%
0.3	600	1.9%	3.7%	7.3%
0.5	400	2.5%	4.9%	9.8%
0.5	500	2.2%	4.4%	8.8%
0.5	600	2.0%	4.0%	8.0%

TABLE E2. Estimates of very poorly controlled diagnosis precision based on actual sample size of 341

Estimated proportion	Sample size	SE	SE × 1.96	CI width
0.3	341	2.5%	4.9%	9.7%
0.5	341	2.7%	5.3%	10.6%

TABLE E3. Data collected in TENOR I and TENOR II

Collected by study coordinator		Derived variables	
TENOR I/II	TENOR II	TENOR I/II	TENOR II
● Demographics ● Asthma history ● Health care use* ● Comorbid medical conditions ● Medication use† ● Targeted AEs	● Additional comorbid medical conditions ● Additional allergy and asthma medications, biologics	● NHLBI impairment category	● ATS definition of severe exacerbation ● Maximum reversibility
Collected by patient self-report		Laboratory tests	
TENOR I/II	TENOR II	TENOR I/II	TENOR II
● Asthma triggers ● Skin tests (TENOR I only) ● Residential exposures ● Occupational exposures ● Symptoms/control (ATAQ) ● Work productivity (WPAI-Asthma) ● Quality of life (MiniAQLQ)	● Sun exposure ● Additional triggers (air pollution and nontobacco smoke) ● Medication adherence (AAAQ)	● Total IgE level ● Spirometry	● Vitamin D ● Eosinophils ● Basophils ● Specific IgE ● FENO ● Pharmacogenetics

AE, Adverse event.

*Recall period was 3 months in TENOR I and 3 and 12 months in TENOR II.

†Current medications in TENOR I; current or in previous 6 months in TENOR II.

TABLE E4. New comorbidities and medications collected in TENOR II

Comorbidities	
GI comorbidities: ● Eosinophilic esophagitis ● GERD ● History of bariatric surgeries ● Irritable bowel disease Other conditions: ● Food allergy ● Glaucoma ● Increased/ease of bruisability ● Insomnia	Skin comorbidities: ● Acute or chronic urticaria/angioedema ● Chronic idiopathic urticaria Respiratory comorbidities: ● Acute or chronic sinusitis ● Chronic obstructive asthma ● Obstructive sleep apnea ● Restrictive lung disease ● Upper respiratory tract infection ● Nasal polyps ● History of bronchial thermoplasty ● History of nasal polypectomies
Medications	
Long-term medications: ● Inhaled corticosteroids ● Ciclesonide ● Mometasone ● Long-acting β_2-agonists ● Formoterol ● Arformoterol ● Indacaterol ● Combined inhaled corticosteroids and long-acting β_2-agonists ● Budesonide/formoterol ● Mometasone/formoterol Short-acting relief medications: ● Short-acting β_2-agonist ● Levalbuterol Systemic corticosteroids: ● Dexamethasone ● Solumedrol Long-acting anticholinergic/muscarinic antagonists: ● Tiotropium bromide ● Aclidinium bromide Leukotriene modifiers: ● Montelukast Biologics: ● Omalizumab ● Mepolizumab (IL-5 inhibitor) ● Reslizumab (IL-5 inhibitor) ● Lebrikizumab (IL-13 inhibitor) ● Tralokinumab (IL-13 inhibitor) Acute sinusitis antibiotics: ● Amoxicillin (any formulation) ● Amoxicillin/clavulanic acid (any formulation) ● Penicillin (any formulation) ● Cephalosporin (any formulation) ● Azithromycin ● Clarithromycin ● Clindamycin ● Doxycycline ● Fluoroquinolones (any formulation)	Atopic dermatitis medications: ● Tacrolimus ● Pimecrolimus ● Mometasone ● Betamethasone dipropionate ● Hydrocortisone ● Fluticasone ● Triamcinolone ● Fluocinolone ● Desoximetasone ● Desonide Allergic rhinitis medications: ● Intranasal steroids ● Beclomethasone ● Fluticasone (propionate and furoate) ● Fluticasone/azelastine ● Mometasone ● Budesonide ● Flunisolide ● Triamcinolone ● Ciclesonide ● Intranasal nonsteroid medications ● Cromolyn ● Olopatadine ● Azelastine ● Ipratropium ● Oral nonsedating antihistamines ● Cetirizine ● Levocetirizine ● Loratadine ● Desloratadine ● Fexofenadine GERD/GI reflux medications: ● H₂-antagonists ● Famotidine ● Ranitidine ● Cimetidine ● Nizatidine ● Proton pump inhibitors ● Lansoprazole ● Omeprazole ● Pantoprazole ● Rabeprazole ● Dexlansoprazole ● Esomeprazole

TABLE E5. Biomarker values according to level of asthma control

Variable	Well controlled (n = 26)	Not well controlled (n = 116)	Very poorly controlled (n = 197)
Eosinophils (/μL)			
No.	21	100	190
Mean ± SD	167 ± 124	197 ± 135	205 ± 150
Median (interquartile range)	100 (100)	200 (200)	200 (200)
Minimum-maximum	0-400	0-700	0-800
Basophils (/μL)			
No.	21	100	190
Mean ± SD	43 ± 51	50 ± 52	55 ± 57
Median (interquartile range)	0 (100)	0 (100)	100 (100)
Minimum-maximum	0-100	0-200	0-300
FENO (ppb)			
No.	8	53	113
Mean ± SD	27 ± 19	29 ± 25	29 ± 31
Median (interquartile range)	19 (21)	23 (20)	21 (18)
Minimum-maximum	7-67	6-178	5-273

TABLE E6. WPAI-Asthma and MiniAQLQ subscores (n = 341)

	No.	Value
MiniAQLQ variable, mean subscore $\pm$ SD		
Symptoms	341	4.3 $\pm$ 1.3
Environmental stimuli	341	3.7 $\pm$ 1.7
Emotional function	341	4.3 $\pm$ 1.7
Activity limitation	340	4.6 $\pm$ 1.5
WPAI-Asthma variable, mean $\pm$ SD (%)		
Work time missed	160	6.3 $\pm$ 63.5
Impairment while working	164	10.6 $\pm$ 17.8
Overall work impairment	160	13.3 $\pm$ 34.8
Class time missed	24	0.0 $\pm$ 0.0
Impairment in the classroom	25	8.8 $\pm$ 18.3
Overall classroom impairment	24	9.2 $\pm$ 18.6
Activity impairment	329	21.0 $\pm$ 25.9