Consistently very poorly controlled asthma, as defined by the impairment domain of the Expert Panel Report 3 guidelines, increases risk for future severe asthma exacerbations in The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study

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Background: Identification of patients at risk for asthma exacerbations can assist physicians in addressing disease management and improve asthma-related health outcomes.

Objective: We sought to evaluate whether level of impairment, as defined by the 2007 asthma guidelines, predicts risk for future asthma exacerbations.

Methods: The study included children aged 6 to 11 years (n = 82) and adolescent/adult patients aged 12 years and older (n = 725) from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens study with data representing all components of the impairment domain of the asthma guidelines at baseline, month 12, and month 24. Patients were categorized into 2 cohorts: (1) consistently very poorly controlled (VPC) asthma from baseline through 2 years of follow-up and (2) improved from VPC asthma at baseline (including patients who improved to not well-controlled or well-controlled asthma), with improvement maintained through 2 years of follow-up. Odds ratios (ORs) and 95% CIs for risk of asthma exacerbations at month 30 were generated by using multivariable logistic regression by age group.

Results: After adjustment, children with consistently VPC asthma over the 2-year period demonstrated a 6-fold increased risk of hospitalization, emergency department visit, or corticosteroid burst (OR, 6.4; 95% CI, 1.2-34.5) compared with the improved group. Adolescent/adult patients with consistently VPC asthma were more likely to have a corticosteroid burst (OR, 2.8; 95% CI, 1.7-4.8) or have a hospitalization, emergency department visit, or corticosteroid burst (OR, 3.2; 95% CI, 1.9-5.3).

Conclusions: Consistently VPC asthma, as defined by the impairment domain of the 2007 asthma guidelines, is strongly predictive of future asthma exacerbations. (J Allergy Clin Immunol 2009;124:895-902.)

Key words: *Asthma, asthma guidelines, impairment domain, risk, exacerbations, health care use, asthma control, The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens study*

Asthma affects more than 22 million persons in the United States, including 16.1 million adults and 6.8 million children.[1] Currently, asthma represents the most common chronic disease in children,[2] and its global prevalence is projected to increase substantially over the next 2 decades.[3,4] The physical, emotional, social, professional, and economic challenges conferred by asthma can have a substantial effect on patients' overall quality of life.[5-7] In addition, asthma imposes a significant burden on the US health care system; total costs of asthma in the United States in 1998 were estimated at $12.7 billion, of which 58% represented direct

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Supported by Genentech, Inc, and Novartis Pharmaceuticals Corporation.

Disclosure of potential conflict of interest: J. E. Fish is an employee of Genentech. R. S. Zeiger is a consultant for Aerocrine, AstraZeneca, Genentech, GlaxoSmithKline, Merck, Novartis, and Schering and has received research support from Aerocrine, Sanofi-Aventis, Genentech, Merck & Co, and GlaxoSmithKline. S. J. Szefler is a consultant for GlaxoSmithKline, Genentech, and Merck and has received research support from the National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute (NHLBI) Childhood Asthma Management Program (CAMP), NHLBI Childhood Asthma Research and Education, the NIH/NHLBI Asthma Clinical Research Network, the NIH/National Institute of Allergy and Infectious Diseases Inner City Asthma Consortium, Roos Pharmaceuticals, and GlaxoSmithKline. D. P. Miller is employed by ICON Clinical Research, which received research funding from Genentech. B. E. Chipps has received research support from Genentech, Alcon, and AstraZeneca; has provided expert witness testimony for AstraZeneca regarding Symbicort research; and is a consultant on the speakers' bureau for Sepracor, GlaxoSmithKline, AstraZeneca, Alcon, Genentech, Novartis, Schering-Plough, Aventis, MADA. F. E. R. Simons has received research support from the Canadian Institutes of Health Research. S. T. Weiss is a consultant for Genentech. S. E. Wenzel has received research support from GlaxoSmithKline and is an advisory board member for the Global Initiative for Asthma. L. Borish is a consultant for Genentech, is on the speakers' bureau for Merck, and has received research support from GlaxoSmithKline. E. R. Bleecker is a consultant for AstraZeneca, Boehringer-Ingelheim, Centocor, Genentech, GlaxoSmithKline, Novartis, Pfizer, Wyeth, and Merck and has received research support through Wake Forest University Health Sciences, Aerovance, Amgen, AstraZeneca, Boehringer-Ingelheim, Centocor, Ception, Genentech, GlaxoSmithKline, Novartis, Novartis, Pfizer, and Wyeth. T. Haselkorn has been a paid consultant to Genentech since December 2002.

Received for publication December 23, 2008; revised July 6, 2009; accepted for publication July 24, 2009.

Available online October 8, 2009.

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0091-6749/$36.00

doi:10.1016/j.jaci.2009.07.035

Abbreviations used
ATAQ: Asthma Therapy Assessment Questionnaire
ED: Emergency department
NHLBI: National Heart, Lung, and Blood Institute
NWC: Not well controlled
OR: Odds ratio
TENOR: The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens
VPC: Very poorly controlled
WC: Well controlled

medical expenditures.[8] Asthma costs are shown to be directly related to patients' levels of asthma control, with the highest costs incurred in patients with severe uncontrolled asthma.[9-12] Predicting which patients are at highest risk for increased health care use could facilitate improved clinical management, which in turn could reduce the economic burden of this disease.[13]

Guidelines for the diagnosis and management of asthma from the National Heart, Lung, and Blood Institute (NHLBI) were updated in 2007. These guidelines place greater emphasis on the assessment of asthma control versus asthma severity and use a combination of measures versus any single measure for more consistent evaluation of asthma control.[14,15] Asthma control is characterized by 2 domains: current impairment and future risk.[14,15] The impairment domain addresses the frequency and intensity of symptoms and the functional limitations the patient might be experiencing. It remains to be established whether asthma control, as defined by the impairment component of the guidelines, can predict risk for future asthma exacerbations.

The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study, representing the largest cohort of patients with severe or difficult-to-treat asthma studied to date, provides a unique opportunity to evaluate the association between the impairment domain of the NHLBI guidelines and risk of asthma exacerbations in these patients. The primary objective of this analysis was to determine whether patients with consistently very poorly controlled (VPC) asthma, as defined by the impairment domain of the current NHLBI guidelines, have a higher risk of future asthma exacerbations compared with patients who improved from having VPC asthma. The secondary objective was to identify specific demographic and clinical factors predictive of consistently VPC asthma. We hypothesized that patients with consistently VPC asthma would have a higher risk of future asthma exacerbations compared with patients who improved from VPC asthma. This hypothesis tests whether the 2007 asthma guidelines' impairment domain is a robust paradigm in which to classify a patient's asthma control to identify patients at risk for future asthma exacerbations. Additionally, we hypothesized that specific demographic and clinical characteristics that were previously found to be predictive of asthma exacerbations[16] would be associated with having consistently VPC asthma.

METHODS

Study population

Full details of the TENOR study have been reported elsewhere.[17,18] This was a 3-year (2001-2004), multicenter, prospective cohort study of 4756 patients aged 6 years or more with severe or difficult-to-treat asthma. Inclusion/exclusion criteria are described in Table E1 (available in this article's Online Repository at www.jacionline.org). Patients were enrolled from diverse geographic sites in the United States to reflect the variety of different settings in which patients with asthma receive care, including managed care organizations, clinics associated with academic institutions, and community or group practices. No treatment intervention was involved; all enrolled patients continued to receive asthma medication as directed by their asthma specialist.[17] The TENOR study design and protocol were approved by a central institutional review board and, as necessary, by individual institutional review boards.

Data collection

Demographic and clinical data were collected through study coordinator interview and evaluation at semiannual and annual visits. Patient geographic location was classified as urban or rural by zip code, as defined in the Rural Urban Commuting Area classification system.[19-21]

To assess medication use, including long-term controller and quick-relief medications, patients brought their medications to the interview, and current use was noted. Medication adherence was measured by using a proxy from the Asthma Therapy Assessment Questionnaire (ATAQ): "What best describes how you take this medicine now?"

Patients reported health care use for the previous 3 months at study entry and at each 6-month visit within a 3-month window. Histories of allergic rhinitis and atopic dermatitis were self-reported by using questions from the American Thoracic Society Division of Lung Disease.[22] Total serum IgE levels were measured at baseline by using commercially available assays meeting 510(k) US Food and Drug Administration approval and calibrated to the World Health Organization's Second International Reference Preparation for Human Serum IgE (WHO IRP 75/502).

Assessment of asthma control cohorts

Because the TENOR database does not contain all requisite components (ie, reduction in lung growth or treatment-related adverse effects) to sufficiently map to the risk domain of the guidelines and exacerbation data were collected at specific intervals within a 3-month window, this analysis focused solely on the impairment domain to ascertain asthma control (see Tables E2 and E3 in this article's Online Repository at www.jacionline.org).[14,15] Patients were included in the current analysis if they had data available for all components of the NHLBI guidelines' impairment domain at baseline, month 12, and month 24. Two main patient cohorts were analyzed based on the impairment domain of the NHLBI guidelines (Fig 1): cohort 1 consisted of patients who had VPC asthma at baseline and had consistently VPC asthma through 2 years of follow-up, and cohort 2 included patients who had VPC asthma at baseline but improved and maintained this improvement through 2 years of follow-up. Patients included in the improved cohort could have followed any one of the following combinations: (1) VPC asthma at baseline to not well-controlled (NWC) asthma at month 12 and NWC asthma at month 24; (2) VPC asthma at baseline to NWC asthma at month 12 and well-controlled (WC) asthma at month 24; (3) VPC asthma at baseline to WC asthma at month 12 and NWC asthma at month 24; or (4) VPC asthma at baseline to WC asthma at month 12 and WC asthma at month 24.

Assessment categories included symptoms, nighttime awakenings, interference with normal activity, short-acting β_2-agonist use for symptom control, and lung function, as determined based on measurement of FEV_1 or peak flow. Data for the first 3 categories (symptoms, nighttime awakenings, and interference with normal activity) were captured in the TENOR study at baseline and annually by using the Pediatric Asthma Quality-of-Life Questionnaire with Standardized Activities[23,24] for children aged 6 to 12 years and the Juniper Mini Asthma Quality of Life Questionnaire (Mini-AQLQ)[23,25,26] for patients aged 13 years and older. Although these age ranges do not correspond precisely to the age groups for which these 2 instruments were developed, the individual items collected provided the requisite data to map the questionnaire responses accurately to the asthma guidelines (see detailed footnotes for Tables E2 and E3). Use of short-acting β_2-agonists for symptom control was captured as part of medication use data in the TENOR study, and FEV_1 or peak flow was measured at annual visits only by using spirometry in accordance

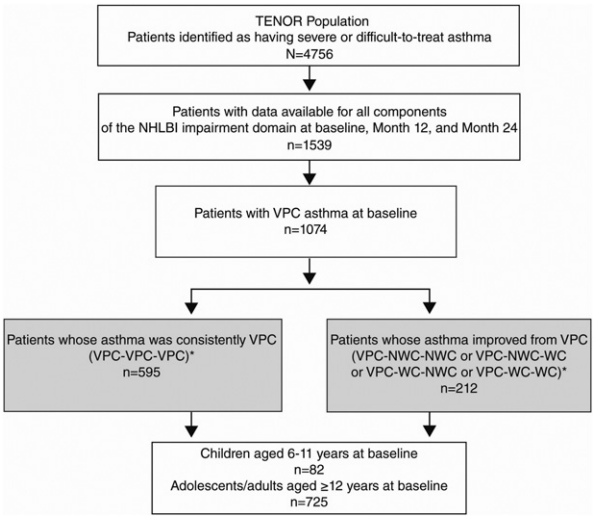

FIG 1. Study population. Two hundred sixty-seven of 1074 patients whose pattern of asthma control was VPC-VPC-(N)WC or VPC-N(WC)-VPC were excluded. *Asthma control assessments at baseline, month 12, and month 24.

with American Thoracic Society guidelines.[27] Participating study sites were required to have a certified instrument calibrated daily for performing flow spirometry.

Asthma control was also assessed, as per the guidelines, by using a validated questionnaire, the ATAQ. The ATAQ is a brief, self-administered questionnaire that evaluates asthma symptoms and level of asthma control,[28,29] provides a simple index of the number of asthma control problems (0-4), and demonstrates significant correlation with other measures of impairment, such as health care use and quality-of-life questionnaires.[28,29]

Primary outcomes

Oral corticosteroid courses are recommended by the Expert Panel Report 3 guidelines as one of the factors in assessing risk, and we have examined this risk factor in this report. In addition, given the severe or difficult-to-treat TENOR cohort, we thought it important to capture even more severe events/exacerbations, such as emergency department (ED) visits and hospitalizations, to better understand the risk burden of asthma on this cohort. In the interest of fully separating the outcome assessment period from the 2-year interval used to define the cohorts, primary outcomes were the occurrence of asthma exacerbations at the month 30 visit, which was defined as the number of hospitalizations, ED visits, or corticosteroid bursts in the previous 3 months (ie,, months 27-30). In addition, 2 different composite exacerbation measures were calculated: a hospitalization/ED visit composite and a hospitalization/ED visit/corticosteroid burst composite. Composite measures were constructed such that the least common measures of exacerbation, and presumably the most severe, were always included as part of the composite. This approach ensured that they would not be considered as nonevents in analyses of more common and less serious outcomes.

Statistical analysis

Based on the age groupings from the 2007 NHLBI guidelines, children (aged 6-11 years, n = 82) and adolescents/adults (aged ≥12 years, n = 725) were analyzed separately. Demographic and clinical characteristics were assessed by using descriptive statistics. *P* values comparing between-cohort differences were computed by using χ^2 tests for categorical variables and 2-sample *t* tests for continuous variables. Differences in outcomes between the 2 cohorts (consistently VPC asthma vs improved from VPC asthma) were assessed by using *P* values derived from the Fisher exact test (for patients aged 6-11 years) or χ^2 test (for patients aged ≥12 years). Multivariable logistic regression models assessing risk of asthma exacerbations were generated with the following covariates: recent exacerbation (3 months before enrollment), age, presence of chronic obstructive pulmonary disease (adolescents/adults cohort only), sex, allergic triggers (pollen, animal dander, dust, or mold), nonallergic triggers (emotional stress or sinus infection), race/ethnicity (white or nonwhite), and body mass index (≥95th percentile for children and <30 or ≥30 kg/m^2 for adults). The covariates included in multivariable models were prespecified based on prior analyses.[16] In a separate analysis in the cohort aged 12 years and older, odds ratios (ORs) and 95% CIs were used to identify demographic and clinical predictors of consistently VPC asthma.

RESULTS

Patient characteristics

Baseline demographics and clinical characteristics for children and adolescents/adults in each cohort (consistently VPC asthma and improved from VPC asthma) are shown in Tables I and II. Most (62.2%) of the children were consistently classified as having VPC asthma. Children who had VPC asthma were less likely to have private insurance ($P = .028$) and more likely to be treated by a pulmonologist ($P = .003$). Among the clinical measures (Table II), children who were consistently classified as having VPC asthma were more likely to have a history of atopic dermatitis ($P = .019$) than children in the improved from VPC asthma group. Children who were consistently classified as having VPC asthma were taking more long-term controller medications than those who improved from VPC asthma (patients receiving ≥3 long-term controllers: 78.4% vs 54.8%, respectively; $P = .008$). Medication adherence did not differ between the 2 cohorts.

In the adolescent/adult group, 75% were consistently classified as having VPC asthma. Patients with VPC asthma were older ($P = .006$) and more likely to be black ($P = .003$), to be current smokers ($P = .014$), to have nonprivate insurance ($P < .0001$), and to be treated by a pulmonologist ($P = .006$). Patients with VPC asthma also had a longer duration of asthma ($P < .0001$), higher mean body mass index ($P = .037$), and lower race-adjusted postbronchodilator percent predicted FEV_1 ($P < .0001$). Of note was the large proportion of patients with allergic rhinitis in both cohorts (70.8% in the VPC asthma cohort and 77.3% in the improved from VPC asthma cohort). The number of long-term controllers did not differ; most patients in both cohorts were using 3 or more long-term controllers. Medication compliance did not differ between the 2 cohorts.

Association of poor asthma control with outcomes

In multivariable analyses adjusted for the number of long-term controllers and other variables (Fig 2), children who were consistently classified as having VPC asthma had more than a 6-fold increased risk of a hospitalization, ED visit, or corticosteroid burst (OR, 6.4; 95% CI, 1.18-34.5) compared with children who improved from VPC asthma. Risks of individual measures of asthma exacerbations were not performed in this age group because of the small number of children. Adolescents and adults who were consistently classified as having VPC asthma were more than 3 times more likely to have a hospitalization, ED visit, or corticosteroid burst compared with adolescents and adults who improved from VPC asthma; the consistently VPC asthma group also showed an increased risk of corticosteroid burst (OR, 2.8; 95% CI, 1.71-4.75).

TABLE I. Patients' demographics at baseline related to consistently VPC asthma or improved from VPC asthma*

Characteristic	Children (6-11 y)			Adolescents and adults (≥12 y)		
	Consistently VPC asthma	Improved from VPC asthma	P value	Consistently VPC asthma	Improved from VPC asthma	P value
Total patients, no. (%)	51 (62.2)	31 (37.8)		544 (75.0)	181 (25.0)	
Age at baseline (y), mean (SD)	8.8 (1.7)	9.2 (1.8)	.308	49.8 (16.2)	45.9 (17.2)	.006
Sex, no. (%)						
Female	15 (29.4)	11 (35.5)	.567	371 (68.2)	124 (68.5)	.938
Male	36 (70.6)	20 (64.5)		173 (31.8)	57 (31.5)	
Race/ethnicity, no. (%)						
White	24 (47.1)	23 (74.2)	.023	423 (77.8)	158 (87.3)	.003
Black	18 (35.3)	3 (9.7)		91 (16.7)	12 (6.6)	
Other	9 (17.6)	5 (16.1)		30 (5.5)	11 (6.1)	
Education, no. (%)						
≤ High school	NA	NA		169 (33.1)	42 (26.1)	.165
Some college/trade school				179 (35.1)	57 (35.4)	
College graduate or advanced degree				162 (31.8)	62 (38.5)	
Urban/rural, no. (%)						
Urban core area	36 (72.0)	23 (74.2)	.485	408 (76.0)	136 (75.6)	.922
Suburban area	4 (8.0)	3 (9.7)		43 (8.0)	17 (9.4)	
Large town area	4 (8.0)	0 (0.0)		39 (7.3)	13 (7.2)	
Small town and isolated rural area	6 (12.0)	5 (16.1)		47 (8.8)	14 (7.8)	
Smoking status, no. (%)						
Never	NA	NA		315 (61.8)	105 (65.2)	.014
Former				174 (34.1)	56 (34.8)	
Current				21 (4.1)	0 (0.0)	
Health care provider, no. (%)						
Private insurance	31 (60.8)	26 (83.9)	.028	338 (62.1)	156 (86.2)	<.0001
Nonprivate insurance	20 (39.2)	5 (16.1)		206 (37.9)	25 (13.8)	
Treatment setting, no. (%)						
Pulmonologist	42 (82.4)	16 (51.6)	.003	179 (33.6)	41 (22.7)	.006
Allergist	9 (17.6)	15 (48.4)		353 (66.4)	140 (77.3)	

NA, Not applicable.
*Asthma control status was defined by the impairment domain of the NHLBI guidelines.

Demographic and clinical variables predictive of remaining in the VPC asthma cohort

Nonprivate insurance, treatment by a pulmonologist, postbronchodilator actual FEV_1/forced vital capacity ratio, allergic triggers, and postbronchodilator percent predicted forced vital capacity were each independent risk factors for having consistently VPC asthma (Fig 3). The likelihood of consistently VPC asthma increased by 40% for each added allergic trigger, by 90% for each 10% decrease in postbronchodilator actual FEV_1/forced vital capacity ratio, and by 30% for each 10% decrease in postbronchodilator percent predicted forced vital capacity.

DISCUSSION

This analysis of TENOR study patients with severe or difficult-to-treat asthma demonstrated that having consistently VPC asthma over time, as defined by the impairment domain of the 2007 NHLBI asthma guidelines, predicts future risk for asthma exacerbations. This was evidenced by significantly higher risks for the composite outcome of hospitalizations, ED visits, or corticosteroid bursts in both children and adolescents/adults who had consistently VPC asthma compared with patients who improved from VPC asthma. These data support the 2007 asthma guidelines' impairment domain as a rigorous framework in which to classify a patient's asthma control and identify patients at risk for future asthma exacerbations. We also identified demographic and clinical factors predictive of consistently VPC asthma, specifically type of insurance, treating physician, lung function measures, and allergic triggers.

Although this study focused on applying the current asthma guidelines to predict future asthma exacerbations, other studies have approached prediction of exacerbations differently, including assessment of quality-of-life measures, psychometric tools, risk factors for hospitalization, and pharmacy data.[30-33] A number of studies have focused on prior asthma exacerbations as predictors of future exacerbations. In a separate TENOR analysis involving patients aged 12 years or more, patients with a recent severe exacerbation (requiring an ED visit or night of hospitalization in the prior 3 months) were at a 3-fold greater risk of future exacerbation compared with patients without a recent severe exacerbation after adjusting for asthma control, 3 different guideline measures of severity, and demographic and clinical characteristics.[16] A recent analysis indicated that prior history of an asthma exacerbation requiring a systemic corticosteroid was predictive of a future exacerbation, whereas individual assessment of several physiologic and biologic markers had poor positive predictive value.[34] Several other studies have also indicated that a history of prior hospitalization or ED visits is a good predictor of hospitalization or ED visits.[35-38]

In addition to prior exacerbations, asthma control, assessed solely by using a validated instrument, such as the ATAQ, has been used to predict future asthma exacerbations. The TENOR Study Group demonstrated that adult asthmatic patients with 3 or 4 asthma control problems (barriers to optimal asthma

TABLE II. Patients' clinical characteristics at baseline related to consistently VPC asthma or improved from VPC asthma*

Characteristic	Children (6-11 y)			Adolescents and adults (≥12 y)		
	Consistently VPC asthma (n = 51)	Improved from VPC asthma (n = 31)	*P* value	Consistently VPC asthma (n = 544)	Improved from VPC asthma (n = 181)	*P* value
Duration of asthma (y), mean (SD)	6.4 (2.3)	5.5 (2.9)	.111	28.2 (17.5)	21.5 (16.0)	<.0001
Body mass index (kg/m_2), means (SD)	20.0 (5.1)	20.2 (4.8)	.828	31.0 (8.2)	29.6 (7.0)	.037
Not obese† (children) or <30 kg (adults), no. (%)	38 (74.5)	24 (77.4)	.766	300 (55.1)	111 (61.3)	.146
Obese (children) or ≥30 (adults), no. (%)	13 (25.5)	7 (22.6)		244 (44.9)	70 (38.7)	
Comorbid condition (COPD/emphysema/ bronchitis), no. (%)						
Yes	NA	NA		224 (41.2)	67 (37.0)	.323
No				320 (58.8)	114 (63.0)	
History of atopic dermatitis, no. (%)						
Yes	10 (19.6)	0 (0.0)	.019	78 (14.3)	18 (9.9)	.173
No	30 (58.8)	24 (77.4)		349 (64.2)	129 (71.3)	
Uncertain	11 (21.6)	7 (22.6)		117 (21.5)	34 (18.8)	
History of allergic rhinitis, no. (%)						
Yes	27 (52.9)	19 (61.3)	.711	385 (70.8)	140 (77.3)	.177
No	6 (11.8)	2 (6.5)		36 (6.6)	7 (3.9)	
Uncertain	18 (35.3)	10 (32.3)		123 (22.6)	34 (18.8)	
IgE at baseline (IU/mL)						
Geometric mean	253.6	199.9	.558	93.6	75.2	.144
95% CI	156.0-412.4	106.8-374.0		81.0-108.1	57.9-97.8	
Median (range)	299.2 (8-12,252)	246.6 (8-3199)		95.0 (1-14,114)	103.0 (1-5575)	
Race-adjusted postbronchodilator percent predicted FEV_1, mean (SD)	92.3 (19.9)	97.1 (12.9)	.263	67.6 (22.0)	84.9 (16.4)	<.0001
Has your doctor prescribed long-term controllers for you?, no. (%)						
Yes	37 (97.4)	27 (100.0)	.999	521 (95.8)	175 (96.7)	.789
No	1 (2.6)	0 (0.0)		11 (2.0)	4 (2.2)	
Unsure	—			12 (2.2)	2 (1.1)	
If yes, medication compliance, no. (%)						
I take it every day.	32 (86.5)	22 (81.5)	.261	473 (90.8)	157 (89.7)	.343
Some days I take it, but other days I do not.	4 (10.8)	1 (3.7)		29 (5.6)	15 (8.6)	
I used to take it, but now I do not.	0 (0.0)	2 (7.4)		10 (1.9)	1 (0.6)	
I only take it when I have symptoms.	1 (2.7)	2 (7.4)		9 (1.7)	2 (1.1)	
Long-term controllers, no. (%)						
0	—	—	—	3 (0.6)	0 (0.0)	.613
1	0 (0.0)	4 (12.9)	.008	31 (5.7)	10 (5.5)	
2	11 (21.6)	10 (32.3)		176 (32.4)	67 (37.0)	
≥3	40 (78.4)	17 (54.8)		334 (61.4)	104 (57.5)	

COPD, Chronic obstructive pulmonary disease; *NA*, not applicable.
*Asthma control was defined by the impairment domain of the NHLBI guidelines.
†For children, obese was defined as the 95th percentile or greater.

management) were at significantly greater risk for unscheduled office visits, oral corticosteroid bursts, ED visits, or hospitalization.[13] Vollmer et al[28,39] observed that asthma control, as measured with the ATAQ, was a significant predictor of health care use, even after adjustment for prior health care and medication use.[39] Sharma et al[40] used a clinical status questionnaire based on the 2007 NHLBI guidelines, which indicated that poor asthma control significantly predicted health care use at 3 months among inner-city, black, preschool-aged children. Because control did not significantly predict health care use at the 6-month time point, the authors concluded that frequent patient assessments (every 3 months) were necessary to prevent asthma-related morbidity. It is important, however, to consider the inherent limitations of patient self-reported assessments, such as recall bias and dependence on access to health care.[41-45]

Given the number and variety of studies that have been conducted, it is challenging to determine which measures or tools are best suited to evaluate risk for asthma exacerbations.[46] It is unclear how these different measures relate to one another or to patients' perceptions of control. This analysis indicates that a broad assessment of asthma control, using several different measures in concert, is a strong predictor of future exacerbations. In addition, the 2007 NHLBI guidelines differ from previous approaches in that they emphasize the ongoing monitoring of asthma control to guide the therapeutic approach, rather than focusing on a single assessment of disease severity, which can vary with the instrument used and might not truly reflect a patient's asthma control, as observed in a previous TENOR analysis.[47] The new guidelines clarify and emphasize the distinction between asthma severity, the intrinsic intensity of the disease, and asthma control, which can vary over time. This new treatment paradigm, which places increased emphasis on achieving good asthma control, provides a clear framework by which physicians can assess control (current impairment domain) and evaluate future risk (risk for exacerbations). As this TENOR analysis shows, assessment of asthma control (as defined by the impairment component

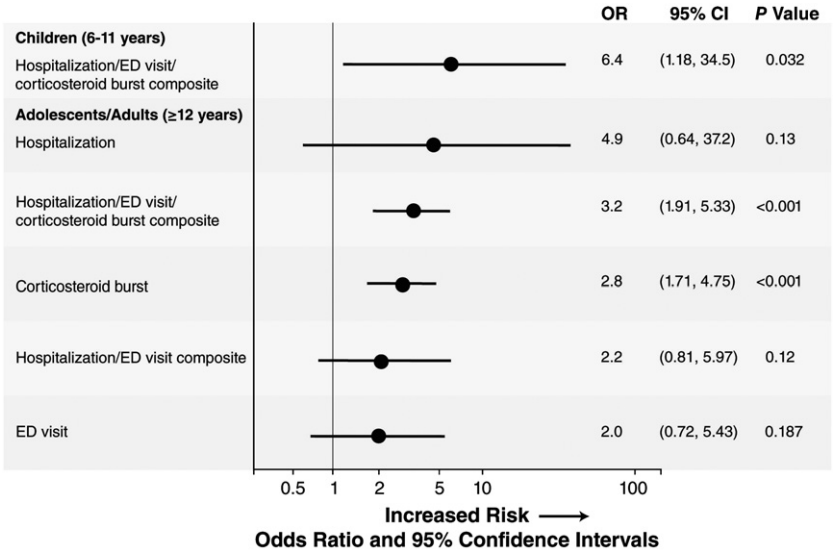

FIG 2. Risk of asthma exacerbations at the month 30 visit associated with consistently VPC asthma as defined by impairment domain of the NHLBI guidelines. Final adjusted models for hospitalization and ED visits include prior hospitalizations or ED visits, number of long-term controllers, body mass index, allergic triggers, nonallergic triggers, percent predicted forced vital capacity, race/ethnicity, and age. Final adjusted models for corticosteroid bursts include prior corticosteroid burst, chronic obstructive pulmonary disease, nonallergic triggers, percent predicted FEV_1/forced vital capacity ratio, race/ethnicity, and age.

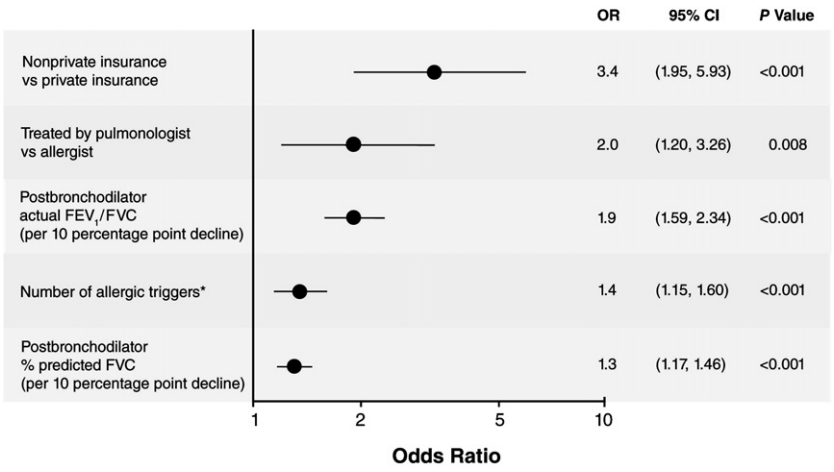

FIG 3. Demographic and clinical factors predictive of consistently VPC asthma as defined by the impairment domain of the NHLBI guidelines. *Allergic triggers considered were pollen, animal dander, dust, and mold. **Predictive factors that were statistically significantly associated with consistently poorly controlled asthma are shown.

of the 2007 NHLBI guidelines) predicted risk for future asthma exacerbations in patients with severe or difficult-to-treat asthma. Through monitoring of the impairment domain (eg, symptoms, nighttime awakenings, short-acting β_2-agonist use, interference of symptoms with normal activity, and lung function), physicians might have the opportunity to reduce patients' risks of exacerbations.[14,15] However, it remains to be shown whether such monitoring, combined with a guideline-directed, stepwise treatment approach, can reduce impairment for the majority of patients.

Importantly, adjustment for medication use did not explain the increased risk of asthma exacerbations in the consistently VPC group, nor were any differences in self-reported medication adherence observed. Similarly, in a recent study approximately half of patients experienced an exacerbation, despite treatment with long-term controllers.[34] In the current analysis most patients were taking 2 to 3 long-term controller medications, with those in the VPC group taking a similar or greater number of long-term medications compared with those in the improved from VPC

group. However, there was minimal effect on impairment: 39% of patients remained in the VPC group, and only 14% demonstrated consistent improvement; thus 85% of all patients with severe or difficult-to-treat asthma continued to have very poorly or poorly controlled disease for the duration of this study. This suggests that asthma in the consistently VPC asthma group might be intrinsically more severe and raises the possibility of resistance to medications, an evolving paradigm in asthma research.

In this analysis specific demographic and clinical characteristics that independently predict which patients are at risk for consistently VPC asthma were identified. Nonprivate insurance, treatment by a pulmonologist, postbronchodilator actual FEV_1/forced vital capacity ratio, allergic triggers, and postbronchodilator percent predicted forced vital capacity were each independent risk factors for consistently VPC asthma. Although it is important to note that TENOR study patients treated by pulmonologists have more severe disease than those treated by allergists,[48] identifying specific factors at the patient level might prove valuable in helping clinicians develop treatment strategies. For example, the likelihood of patients continuing to have consistently VPC asthma increased by 40% for each added allergic trigger, including pollen, animals, dust, and mold. Physicians and patients should be aware that exposure to an increasing number of allergic triggers has evaluable and quantifiable risks to maintaining asthma control.

This analysis included the largest database currently available for severe or difficult-to-treat asthma, encompassing 283 study sites from diverse geographic regions managed by more than 400 pulmonologists and allergists. The sample size and breadth of the variables measured allowed a unique opportunity to analyze an array of clinical and patient-reported outcomes within the context of the NHLBI guidelines. To our knowledge, this analysis is the first to apply the components of the impairment domain of the updated asthma guidelines to assess the effect of long-term asthma control on the future risk of asthma exacerbations.

This analysis had several limitations. The TENOR database does not have the necessary components (ie, reduction in lung growth or treatment-related adverse effects) to sufficiently map to the risk domain of the NHLBI guidelines. In addition, health care use data collection captured asthma exacerbations at specific intervals within a 3-month window. Thus our findings are based solely on the impairment domain of the guidelines. Exacerbation dates were not collected, and the number of exacerbations was collected only for two 3-month windows within each 1-year period. Thus a more sophisticated and perhaps informative analysis, such as a time-to-event analysis, was not possible with the available data and limited number of observations.

These study findings are representative of specialist care in the United States and might not be representative of asthma in the general population or of asthmatic patients in primary care practices. Some information was obtained by means of self-report, which can vary with the patient's ability to recall information. Although the analysis controlled for numerous confounders, it is not possible to rule out residual confounding from as-yet unidentified factors not measured in the TENOR study. Medication compliance was based on a proxy measure from the self-reported ATAQ, introducing the possibility for error or misclassification of these data. Indeed, medication adherence in this study was high in both cohorts; studies generally show adherence among adults to be at approximately 50%,[49,50] and can also be influenced by socioeconomic factors and severity of disease.[51] Moreover, self-reported adherence is considerably higher than objectively-reported adherence.[52] Finally, the analysis included relatively few children, hampering our ability to perform all analyses and possibly to detect differences in this cohort.

To our knowledge, this is the first analysis to assess asthma control within the context of the 2007 asthma guidelines in a large cohort of patients with severe or difficult-to-treat asthma. In the current analysis assessment of asthma control (as defined by the impairment component of the updated NHLBI guidelines) predicted risk for future asthma exacerbations. Thus with respect to assessing asthma control and evaluating future risk, the current guideline-directed approach might provide clinicians with a straightforward means by which to assess patient status. Several variables were independently associated with consistently VPC asthma: number of allergic triggers, postbronchodilator forced vital capacity, postbronchodilator actual FEV_1/forced vital capacity ratio, health insurance, and treating specialist. Future studies might examine the individual components of asthma control (eg, symptoms, nighttime awakenings, and exacerbations requiring oral corticosteroid bursts) to determine which of these best predicts the risk of poor clinical outcomes in asthmatic patients.

In conclusion, the current analysis suggests that assessing asthma control based on the impairment domain of the Expert Panel Report 3 guidelines, which includes a variety of clinical and patient-reported outcome measures assessed on an ongoing basis, can predict future asthma exacerbations. Such information can assist physicians in proactively addressing individual disease management needs and can ultimately help improve asthma-related health outcomes.

We thank Genentech, Inc, and Novartis Pharmaceuticals Corporation for writing assistance with this article.

Clinical implications: Asthma control, as defined by the impairment domain of the 2007 asthma guidelines using a variety of clinical and patient-reported outcome measures, can predict future asthma exacerbations.

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TABLE E1. Inclusion/exclusion criteria for the TENOR study

Inclusion criteria
Have "severe" or "difficult-to-treat" asthma in the opinion of the physician
Have been receiving care from current physician/provider for ≥1 year
Must be ≥6 years old
Must be able to read and understand English
In addition, subjects must meet at least 1 of the following criteria:
During the past 12 months, had ≥2 unscheduled care visits for asthma
During the past 12 months, had ≥2 steroid bursts
Currently using ≥3 medications to control asthma
Currently requires chronic daily high doses of inhaled steroids or ≥5 mg/d oral prednisone
Exclusion criteria
Heavy smoker (≥30 pack-years)
Primary diagnosis of cystic fibrosis
Severe cardiovascular disease (New York Heart Association class II or greater)
Cancer (not including nonmelanoma skin cancer or subjects whose cancer has been clear or in remission for ≥5 years)
Severe psychiatric disorder (not including anxiety or depression)
Significant systemic disease (<2- to 3-year life expectancy)
Known drug abuser

TABLE E2. NHLBI impairment assessment of asthma control in patients 5 to 11 years of age[E1]

Assessment of impairment	Classification of asthma control (children 5-11 y)			TENOR assessment (patients 6-12 y)
	WC asthma	NWC asthma	VPC asthma	
Symptoms	≤2 d/wk but not more than once daily	>2 d/wk or multiple times on ≤2 d/wk	Throughout the day	PAQLQ(S)*
Nighttime awakenings	≤1 time/mo	≥2 times/mo	≥2 times/wk	
Interference with normal activity	None	Some limitation	Extremely limited	
Short-acting β_2-agonist use for symptom control	≤2 d/wk	>2 d/wk	Several times daily	Medication use
FEV_1 or peak flow	>80% predicted/personal best	60% to 80% predicted/personal best	<60% predicted/personal best	Spirometry
FEV_1/FVC ratio	>80%	75% to 80%	<75%	

For this study, items numbered 4, 10, 12, 14, 18, and 23 from the patient-reported Pediatric Asthma Quality of Life Questionnaire (PAQLQ) were used to determine the symptom component of the impairment domain of the 2007 NHLBI Guidelines definition of asthma control in children ages 6 to 12 years. Similarly, items numbered 16 and 20 were used to determine the nighttime awakenings component, and items 1, 3, 13, 19, and 22 were used to determine the normal activities interference component. Patients responded to questions such as "In general, how often during the last week did you feel out of breath because of your asthma?" or "How bothered have you been during the last week by wheezing?" on a 7-point ordinal scale, with 1 corresponding to either "all of the time" or "extremely bothered" and 7 corresponding to either "none of the time" or "not bothered." A symptom component score of 1 or 2 ("extremely or very bothered" and "all or most of the time") was used to approximate the VPC category ("throughout the day"), a score of 3 ("quite bothered" and "quite often") was used to approximate the NWC category ("greater than 2 days per Week"), and scores of 4, 5, 6, or 7 ("somewhat, a bit, Hardly at all, or not bothered" and "some, once in a while, hardly any, or none of the time") were used to approximate the WC category ("less than or equal to 2 days per week"). A nighttime awakening component score of 1 or 2 ("extremely or very bothered" and "all or most of the time") was used to approximate the VPC category ("greater than or equal to 2 times per week"), scores of 3 or 4 ("quite or somewhat bothered" and "quite often or some of the time") were used to approximate the NWC category ("greater than or equal to 2 times per month"), and scores of 5, 6, or 7 ("a bit, hardly at all, or not bothered" and "once in a while, hardly any, or none of the time") were used to approximate the WC category ("less than or equal to 1 time per month"). A normal activity interference component score of 1 or 2 ("extremely or very bothered" and "all or most of the time") was used to approximate the VPC category ("extremely limited"); scores of 3, 4, 5, or 6 ("quite, somewhat, a bit, or hardy bothered" and "quite often, some of the time, once in a while, or hardly any of the time") were used to approximate the NWC category ("some limitation"); and a score of 7 ("not bothered" and "none of the time") was used to approximate the WC category ("no limitation"). For each of these components and also the short-acting β-agonist use and lung function components, patients were assigned to one of the 3 asthma control categories. Overall level of asthma control for each patient was assigned based on the most severe impairment category.

PAQLQ(S), Pediatric Asthma Quality-of-Life Questionnaire with Standardized Activities; *FVC*, forced vital capacity.

TABLE E3. NHLBI impairment assessment of asthma control in patients 12 years of age and older[E1]

Assessment of impairment	Classification of asthma control (youths ≥12 y and adults)			TENOR assessment (patients ≥13 y)
	WC asthma	NWC asthma	VPC asthma	
Symptoms	≤2 d/wk	>2 d/wk	Throughout the day	Mini-AQLQ*
Nighttime awakenings	≤2 times/mo	1-3 times/mo	≥4 times/wk	
Interference with normal activity	None	Some limitation	Extremely limited	
Short-acting β_2-agonist use for symptom control	≤2 d/wk	>2 d/wk	Several times daily	Medication use
FEV_1 or peak flow	>80% of predicted value/ personal best	60% to 80% of predicted value/personal best	<60% of predicted value/ personal best	Spirometry
Validated questionnaires				
ATAQ	0	1-2	3-4	ATAQ
ACQ	≤0.75	≥1.5	NA	
ACT	≥20	16-19	≤15	

VPC was defined by impairment assessment per NHLBI guidelines.

Mini-AQLQ, Mini Asthma Quality-of-Life Questionnaire; *ACQ*, Asthma Control Questionnaire; *ACT*, Asthma Control Test; *NA*, not applicable.

*For this study, items numbered 1, 4, 6, and 10 from the patient-reported Mini Asthma Quality of Life Questionnaire (Mini-AQLQ) were used to determine the symptom component of the impairment domain of the 2007 NHLBI Guidelines definition of asthma control in adolescents and adults ages 13 and older. Similarly, item number 8 was used to determine the nighttime awakenings component, and items 12, 13, 14, and 15 were used to determine the normal activities interference component. Patients responded to questions such as "In general, how much of the time during the last 2 weeks did you feel bothered by coughing?" or "How limited have you been during the last 2 weeks doing [social activities] as a result of your asthma?" on a 7-point ordinal scale, with 1 corresponding to either "all of the time" or "totally limited" and 7 corresponding to either "none of the time" or "not at all limited." A symptom component score of 1 or 2 ("all or most of the time") was used to approximate the VPC category ("throughout the day"), a score of 3 ("a good bit of the time") was used to approximate the NWC category ("greater than 2 days per week"), and scores of 4, 5, 6, or 7 ("some, a little, hardly any, or none of the time") were used to approximate the WC category ("less than or equal to 2 days per week"). A nighttime awakening component score of 1 or 2 ("all or most of the time") was used to approximate the VPC category ("greater than or equal to 4 times per week"), a score of 3 ("a good bit of the time") was used to approximate the NWC category ("1 to 3 times per week"), and scores of 4, 5, 6, or 7 ("some, a little, hardly any, or none of the time") were used to approximate the WC category ("less than or equal to 2 times per month"). A normal activity interference component score of 1 or 2 ("totally or extremely limited") was used to approximate the VPC category ("extremely limited"); scores of 3, 4, 5, or 6 ("very, moderate, some, or a little limitation") were used to approximate the NWC category ("some limitation"); and a score of 7 ("not at all limited") was used to approximate the WC category ("no limitation"). For each of these components, in addition to the short-acting β-agonist use, lung function, and validated questionnaire components, patients were assigned to one of the 3 asthma control categories. Overall level of asthma control for each patient was assigned based on the most severe impairment category.