The prevalence of severe refractory asthma

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Background: Severe asthma is characterized by difficulty to achieve disease control despite high-intensity treatment. However, prevalence figures of severe asthma are lacking, whereas longstanding estimates vary between 5% and 10% of all asthmatic patients. Knowing the exact prevalence of severe refractory asthma as opposed to difficult-to-control asthma is important for clinical decision making, drug development, and reimbursement policies by health authorities.
Objective: We sought to estimate the prevalence of severe refractory asthma as defined by the Innovative Medicine Initiative consensus.
Methods: Adult patients with a prescription for high-intensity treatment (high-dose inhaled corticosteroids and long-acting β_2-agonists or medium- to high-dose inhaled corticosteroids combined with oral corticosteroids and long-acting β_2-agonists) were extracted from 65 Dutch pharmacy databases, representing 3% of the population (500,500 inhabitants). Questionnaires were sent to 5,002 patients, of which 2,312 were analyzed. The diagnosis of asthma and degree of asthma control were derived from questionnaires to identify patients with difficult-to-control asthma. Inhalation technique was assessed in a random sample of 60 adherent patients (prescription filling, ≥80%). Patients with difficult-to-control asthma, adherence to treatment, and a correct inhalation technique were qualified as having severe refractory asthma. Results were mirrored to the Dutch population.
Results: Of asthmatic adults, 3.6% (95% CI, 3.0% to 4.1%) qualified for a diagnosis of severe refractory asthma, representing 10.4 patients per 10,000 inhabitants.
Conclusion: The prevalence of severe refractory asthma might be lower than estimated by expert opinion. This implies that currently recognized severe asthma subphenotypes could meet the criteria of rare diseases. (J Allergy Clin Immunol 2015;135:896-902.)

Key words: *Asthma, severe asthma, severe refractory asthma, difficult-to-control asthma, prevalence*

Abbreviations used
ACQ: Asthma Control Questionnaire
COPD: Chronic obstructive pulmonary disease
ICS: Inhaled corticosteroid
IMI: Innovative Medicine Initiative
LABA: Long-acting β_2-agonist
OCS: Oral corticosteroid

Asthma is a chronic disease of the airways, which can vary from mild to very severe.[1] Severe asthma is characterized by difficulty to achieve disease control despite high-dose inhaled glucocorticoids plus long-acting β_2-agonists (LABAs) or oral corticosteroids (OCSs). Over the past decades, the prevalence of severe asthma has been estimated to be around 5% to 10% of the total asthmatic population.[2-4] However, the exact prevalence is not known because of the lack of an accurate and consistent definition of severe asthma. In 2011, the Innovative Medicine Initiative (IMI) published an international consensus statement in which a more accurate definition of severe asthma was proposed. In this statement a clear distinction was made between "difficult-to-control asthma" and "severe refractory asthma."[5] In patients with difficult-to-control asthma, the lack of asthma control is due to other factors than asthma itself, such as nonadherence to treatment or incorrect inhalation technique.[6] On the other hand, on patients with severe refractory asthma, the disease remains uncontrolled despite addressing and removing all possible factors that might aggravate the underlying disease.

Knowing the exact prevalence of difficult-to-control asthma and severe refractory asthma is important from a clinical, health-economics, and regulatory point of view. First, clinicians must be aware of the proportion of patients with severe refractory asthma, as opposed to those with difficult-to-control asthma, because the 2 conditions require different treatments. Second, from a health-economics perspective, defining the exact prevalence of both conditions is necessary to understand the economic burden and how to best use health care resources. Finally, regulatory agencies need to know the proportion of patients who qualify for new targeted treatments. With a low prevalence, severe refractory asthma might qualify for an orphan disease designation.

The Netherlands is an ideal country to measure the relative prevalences of difficult-to-control asthma and severe refractory asthma. Thanks to compulsory health insurance, health care is easily accessible and medication is widely available throughout the country. Medication use is accurately documented by the pharmacies, and there is a close contact between pharmacies and individual patients. Thus the 3 main reasons for lack of asthma control (ie, poor access to health care, nonadherence to therapy, and inadequate inhalation technique) can be quantified. These figures can then be used to distinguish between difficult-to-control asthma and severe refractory asthma.

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TABLE I. Characteristics of patients with asthma and high-intensity treatment

Subjects (n)	929
Female sex	606 (65.2%)
Age (y)*	62.5 ± 16.5
Body mass index (kg/m^2)*	27.0 ± 5.7
Smoking history (pack years)†	0 (0-10)
ACQ score†	1.33 (0-5)
Allergy‡ yes	573 (61.7%)
ICS dose	
500-1000 μg Fluticasone equivalent	351 (37.8%)
>1000 μg Fluticasone equivalent	578 (62.2%)
Adherence ICS (%)†	74.0 (8.2-364.2)
Adherence ICS (%) with and without OCS§	
Prescription for OCS, yes*	82.9 ± 40.8
Prescription for OCS, no*	68.5 ± 32.0

*Mean ± SD.
†Median (range).
‡Self-reported allergic symptoms to common inhaled allergens.
§$P < .001$.

The aim of the present study is to make a reliable estimation of the prevalence of difficult-to-control asthma and severe refractory asthma based on international consensus definitions in a representative setting.[5,7]

METHODS

Design

In this descriptive observational study we used a definition of severe refractory asthma based on recent international consensus criteria[5] and estimated the prevalence of severe refractory asthma. In short, automated dispensing records from 65 community pharmacies in The Netherlands were used to identify all patients with at least 1 prescription for an inhaled corticosteroid (ICS) in 2011. In The Netherlands around 90% of the population obtains their medication from only 1 community pharmacy, enabling collection of complete medication histories of individual subjects over a long period of time.[8]

On the basis of comprehensive questionnaires that were sent to these patients, we classified them into patients with or without asthma. Then we further classified the asthmatic patients into patients with difficult-to-control asthma and those with severe refractory asthma based on the degree of asthma control, adherence rate, and inhalation technique (Table I). The prevalence of severe refractory asthma was then estimated by dividing the number of patients with severe refractory asthma by the total number of patients with asthma in the pharmacy databases (Fig 1).

The study was approved by the hospital medical ethics board (MEC W11-064; NTR no. 3546). The analyses were done with encoded data, which were not traceable to patient information. Patients who were checked on their inhalation technique provided written informed consent.

Selection of patients

Adult patients (age ≥18 years) with at least 1 prescription for an ICS between January 1, 2011, and December 31, 2011, were selected from the registration databases from 65 community pharmacies spread throughout The Netherlands, representing 500,500 inhabitants (3.0% of the Dutch population). Of those inhabitants, 6,519 adults had a prescription for a high-dose ICS (≥1,000 μg/d fluticasone equivalent) plus a LABA or a medium- to high-dose ICS (500-1,000 μg/d fluticasone equivalent) plus chronic OCSs and LABAs. *Chronic OCS* was defined as at least 2 consecutive 3-month prescriptions for systemic corticosteroids (≥5 mg of prednisone equivalent) in 2011. Data from these patients were extracted and entered into a new encoded database. Subsequently, a sample of 5,002 patients with a prescription for high-intensity treatment were sent questionnaires containing questions about demographics (sex, age, height, and weight), respiratory diagnosis as given by the treating physician, smoking history, airborne allergies (house dust mite, cat dander, dog dander, mixed grass pollens, mixed tree pollens, and mixed fungi), childhood pulmonary diseases, adherence with ICS treatment and possible reasons for nonadherence, number of severe asthma exacerbations during the last year, history of sinonasal disease, and current asthma control with the Asthma Control Questionnaire 6 (ACQ6).[9] Of 5,002 patients, 2,643 did not return the questionnaire, and 47 were excluded because they had died or refused to cooperate (n = 33) or did not meet the inclusion criteria (n = 14). Thus data of 2,312 patients were used for further analysis (Fig 1). Responders and nonresponders to the questionnaires were compared with regard to prescription fillings of ICS and OCS use.

Assessment of correct diagnosis

Among the 2,312 patients with a prescription for high-dose ICSs (or OCSs) plus LABAs who completed and returned the questionnaires, a diagnosis of asthma was considered if the patient had a self-reported doctor's diagnosis of asthma or chronic obstructive pulmonary disease (COPD) and had smoked less than 10 pack years. *Nonasthma* was considered if the patient had smoked 10 or more pack years of cigarettes or if the patient had a self-reported diagnosis other than asthma or COPD (eg, sarcoidosis, cystic fibrosis, or bronchiectasis).

Assessment of asthma control

The level of asthma control was assessed by using the criteria for severe asthma as set by the IMI consensus statement.[5] Asthma was considered uncontrolled if the ACQ6 score was greater than 1.5 (according to the cutoff point set by Juniper et al[9]) or the patient had 3 or more exacerbations in the previous year, which was defined as 3 or more prescriptions for a course of OCSs or 1 or more hospitalizations in the previous year.

Assessment of good adherence

Patients were considered adherent if ICS prescription filling was 80% or greater.[10] Prescription refill rates were calculated from prescription records for a 12-month time period.

Assessment of correct inhalation technique

A representative sample of 60 asthmatic patients adherent to high-intensity inhaled asthma treatment (prescription filling, ≥80%) was checked individually for inhalation technique by the pharmacist. For each type of inhaler, among all steps for correct inhalation, decisive steps were determined in advance to distinguish between a correct or incorrect inhalation technique.[11] If patients scored "correct" on all decisive steps, the technique was marked as correct.

Analysis

First, the number of patients with difficult-to-control asthma was calculated from the pharmacy database as the number of patients with a prescription for high-intensity treatment, a diagnosis of asthma, and uncontrolled symptoms or who could only achieve disease control with daily OCSs.

Then the number of patients with severe refractory asthma was calculated as the fraction of patients with difficult-to-control asthma who showed good adherence plus a good inhalation technique.

Finally, the results from the pharmacy databases were mirrored to the Dutch adult asthma population derived from the National Institute for Public Health and the Environment[12] to make an estimation of the prevalence of difficult-to-control asthma and severe refractory asthma in The Netherlands (Fig 2). According to the numbers of the Dutch statistical center (Centraal Bureau voor Statistiek),[13] in 2011, the Dutch population consisted of 12,741,686 adults, of whom 370,019 (2.9%) had asthma.[12] Ninety-five percent CIs of the prevalence of severe refractory asthma were calculated, assuming the fraction of patients with asthma and high-intensity treatment among adults with asthma is a constant.

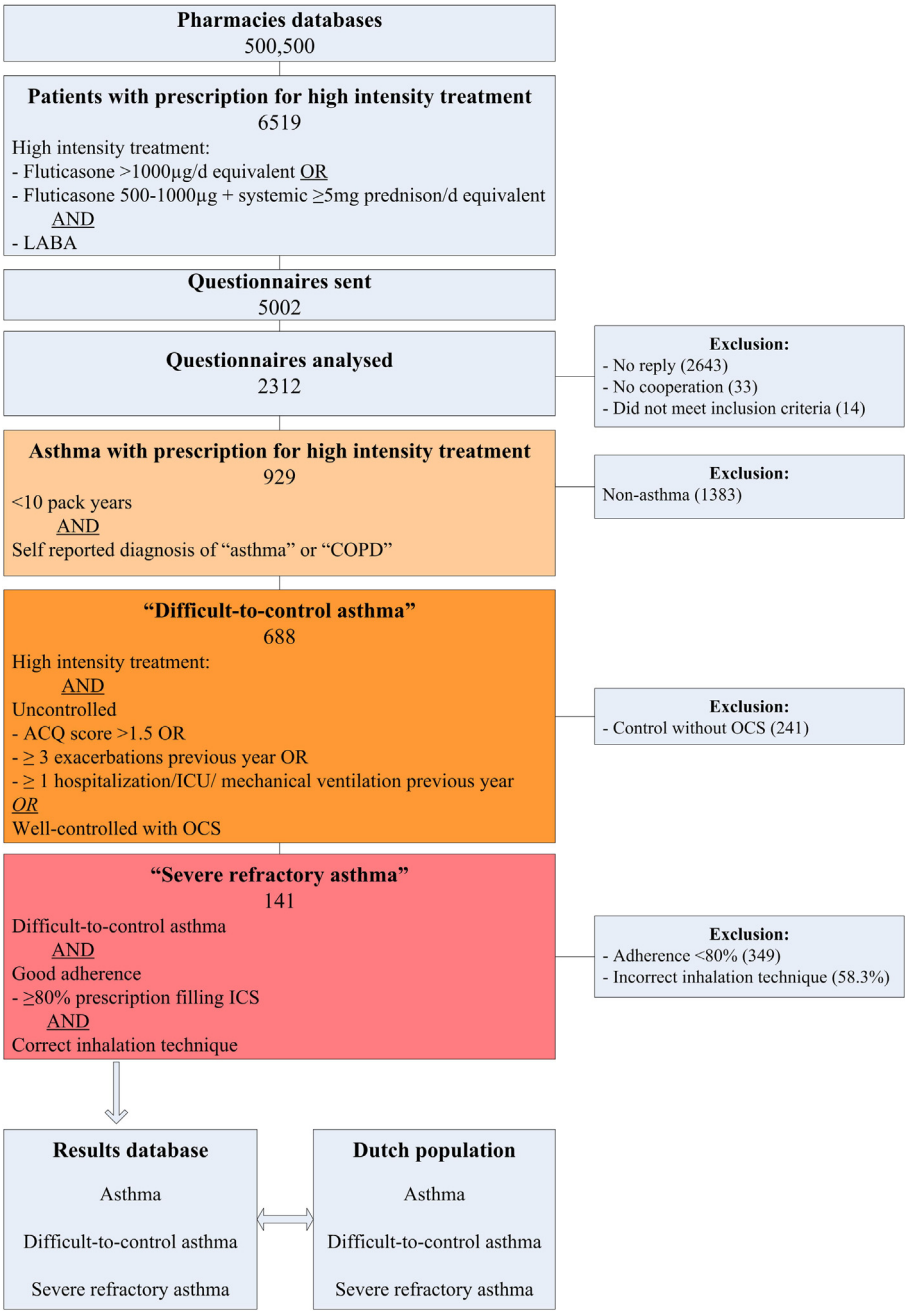

FIG 1. Study design: differentiating steps to get to a diagnosis of severe refractory asthma.

Sensitivity analysis

Because the results might be influenced by assumptions regarding adherence rated and varying percentages of patients using a correct inhalation technique, we performed a sensitivity analysis to calculate the prevalence of severe refractory asthma with very mild or very stringent criteria. To that end, we decreased the rate of adherence from 80% to 70% and varied the percentage of correct inhalation technique from 41% to 10% and 60%, respectively.

RESULTS

Responders and nonresponders to the questionnaire did not differ with respect to OCS prescriptions (median of 0.99 mg [interquartile range, 0.57-2.3 mg] prednisone equivalent for nonresponders and 0.99 mg [interquartile range, 0.57-2.2 mg] for responders, $P = .09$). Adherence to ICSs was significantly lower in nonresponders (mean ± SD, 80% ± 56%) than in responders (mean ± SD, 84% ± 50%; $P < .05$).

Fig 2 shows that of 500,500 subjects included in the pharmacy database, 382,883 (76.5%) were adults. Of these, 6,519 (1.7%) had a prescription for a high-dose ICS (or OCS) plus a LABA. From the questionnaires, it appeared that 40.2% (929/2,312) of these patients qualified for a diagnosis of asthma. Thus 2,618 (40.2% of 6,519) patients included in the pharmacy database qualified for asthma on high-intensity treatment, corresponding to 0.68% of the adult population. Details of these patients are presented in Table I.

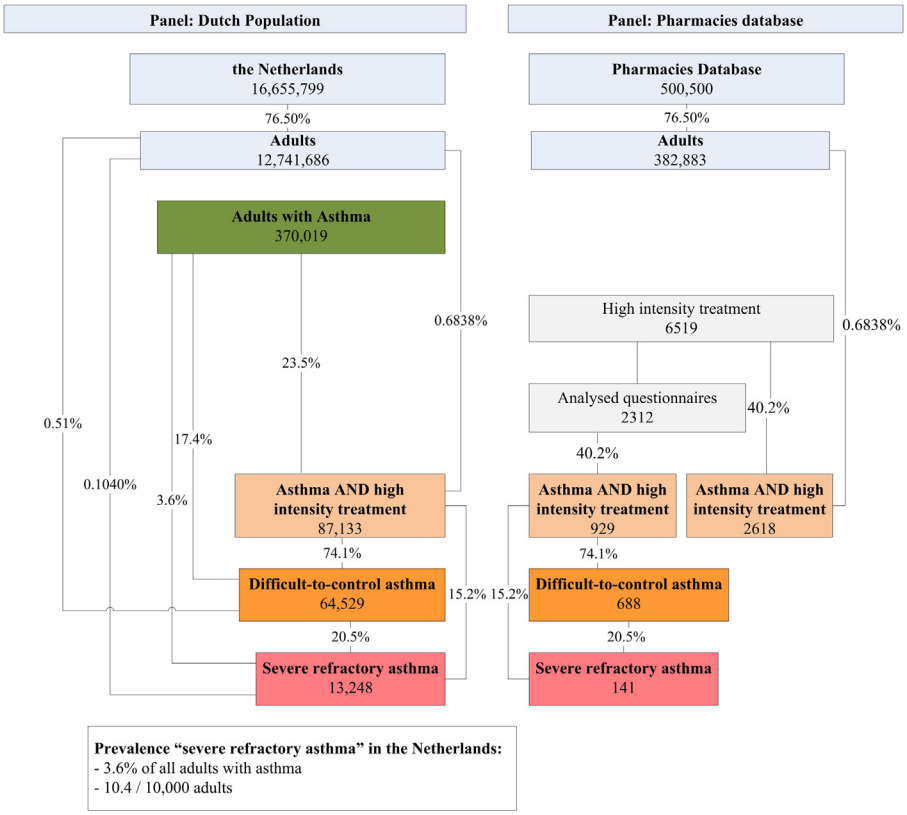

FIG 2. Results. *High-intensity treatment,* high-dose ICS (≥1000 μg/d fluticasone equivalent) plus a LABA or medium- to high-dose ICS (500-1000 μg/d fluticasone equivalent) plus daily OCSs plus a prescription for a LABA.

Prevalence of difficult-to-control asthma

Further analysis of the questionnaires showed that 688 (74.1%) of the 929 asthmatic patients receiving high-intensity treatment qualified for a diagnosis of difficult-to-control asthma: 50.6% had an ACQ score of greater than 1.5, 21.7% had experienced 3 or more exacerbations in 2011, and 21.7% had been hospitalized in 2011.

Knowing that 0.68% of the adult population in the pharmacy database had asthma with high-intensity treatment, we extrapolated this figure to the general Dutch population (panel = Dutch Population). This revealed that 87,133 patients in The Netherlands have asthma on high-intensity treatment and 64,529 have difficult-to-control asthma. This is 17.4% of the total Dutch asthma population (370,019 patients [2.9% of all adults]).

Prevalence of severe refractory asthma

Prescription filling analysis showed that 339 (49.3%) of 688 patients with difficult-to-control asthma were adherent to their (medium-) high-dose ICS with a prescription filling rate of 80% or greater. Then, by using a random sample of 60 patients who were adherent to high-dose ICS treatment, 25 (41.6%) patients showed a correct inhalation technique. Thus only 20.5% of the patients with difficult-to-control asthma qualified for the definition of truly severe refractory asthma. This corresponds to 3.6% (95% CI, 3.0% to 4.1%) of the Dutch adult asthmatic population or 10.4 per 10,000 adult inhabitants.

Sensitivity analysis

The prevalence of severe refractory asthma with the most stringent criteria (ie, adherence, >80%; correct inhalation technique, 10%) was 0.9% (95% CI, 0.6% to 1.1%), whereas the analysis with the mildest criteria (adherence, >70%; correct inhalation technique, 60%) resulted in a prevalence of 6.3% (95% CI, 5.6% to 7.0%).

DISCUSSION

This study shows that 17.4% of the total asthmatic population had difficult-to-control asthma, which was defined as uncontrolled asthma despite the prescription of high-intensity asthma treatment. However, only 20.5% of these patients were adherent to their high-dose ICS prescription and had a correct inhalation technique, corresponding with only 3.6% of the total asthmatic population. This suggests that the prevalence of severe refractory asthma, as defined by international consensus, might be lower than reported in the literature thus far.

This study is the first to assess the relative prevalences of difficult-to-control asthma and severe refractory asthma in a well-documented and transparent health care setting. The current literature is unclear about the exact prevalence of severe refractory asthma, reporting a wide range of prevalences between 5% and 10% of all asthmatic patients.[2-4] Presumably this is due to changing definitions because multiple definitions and criteria on severe asthma have been published in the past decades.[14] Also, the awareness that asthma severity is heavily influenced by factors

TABLE II. Definitions of severe asthma

	IMI international consensus (2011), severe refractory asthma	ATS workshop consensus (2000), refractory asthma	ERS/ATS guideline (2014), severe asthma
Requires that other conditions have been excluded, exacerbating factors treated, and patient believed to be generally adherent	+	+	+
Glucocorticoid treatment (fluticasone equivalent)	Fluticasone >1000 μg/d *OR* Fluticasone >500 μg/d + OCSs ≥50% of year	Fluticasone >880 μg/d *OR* OCSs ≥50% of year	Fluticasone >1000 μg/d *AND/OR* OCSs ≥50% of year
Second controller	LABA	−	LABA/LTRA/theophylline
Further requirements	At least 1 of the following: 1. ACQ score >1.5 2. ≥3 Exacerbations in previous year 3. ≥1 Hospitalization/ICU/mechanical ventilation previous year 4. Controlled asthma achieved with systemic OCS	At least 2 of the following: 1. Requirement for daily treatment with a controller medication 2. Asthma symptoms requiring SABA use on a daily or near-daily basis 3. Persistent airway obstruction (FEV_1 >80% of predicted value; diurnal PEF variability<20%) 4. One or more urgent care visits for asthma per year 5. Three or more oral steroid "bursts" per year 6. Prompt deterioration with <25% reduction in oral or ICS dose 7. Near-fatal asthma event in the past	Uncontrolled asthma *OR* controlled but worsening asthma on tapering corticosteroids

ATS, American Thoracic Society; *ERS*, European Respiratory Society; *ICU*, Intensive care unit; *LTRA*, leukotriene receptor antagonist; *PEF*, peak expiratory flow; *SABA*, short-acting β_2-agonist.

such as poor adherence to treatment and incorrect inhalation technique might have contributed to uncertainty about the real prevalence.[15] Studies have shown that poor adherence to treatment occurs in about half of the patients with difficult-to-control asthma[16-18] and that an inadequate inhalation technique is used in a substantial number of these patients.[11,19-21] Therefore international guidelines and consensus statements clearly differentiate between difficult-to-control asthma and severe refractory asthma. By using a flowchart with several diagnostic steps, including the assessment of adherence to treatment and inhalation technique, a more accurate diagnosis of severe refractory asthma can now be made.[5] The present study has addressed these 2 important factors and shows that the prevalence of truly severe refractory asthma might be lower than previously reported.

The strength of our study is the large number of inhabitants included in the database and the equal distribution of the pharmacies throughout The Netherlands, with coverage of both rural and nonrural areas. Furthermore, the prevalence values were estimated according to the most up-to-date definitions of difficult-to-control asthma and severe refractory asthma, as defined by a group of international experts in the treatment of severe asthma.

Several aspects of our study require further discussion. First, the IMI consensus definition of severe refractory asthma, which we used in the present study, was not identical to the recently published European Respiratory Society/American Thoracic Society guidelines on severe asthma (Table II). In the latter guidelines patients who require treatment with a high-dose ICS to prevent their asthma symptoms from becoming uncontrolled are included. Assuming that all patients with controlled asthma would deteriorate on tapering of corticosteroids, the prevalence of severe asthma according to the European Respiratory Society/American Thoracic Society guidelines would be 4.5% (95% CI, 3.9% to 5.1%) instead of 3.6 (95% CI, 3.0% to 4.1%).

Second, we studied a predominantly European ancestry population in the context of a European National Health Care system. The applicability of our data to other more racially diverse countries with different health care systems might not be the same.

Third, we were not able to confirm the diagnosis of asthma with lung function testing because of the patient anonymity in the study design. This might have resulted in misclassification of some asthmatic patients who actually had COPD. However, by using the most important differentiating characteristics (in particular smoking history) for making a distinction between these respiratory diseases, we believe that the diagnosis was fairly accurate.

Another limitation of our study might be the method of assessing asthma control by using a single measurement of ACQ in presumably trial-naive patients, which might have resulted in errors and inaccuracies. However, if using a definition of severe asthma not including asthma control, the prevalence would have increased only slightly to 4.5% (95% CI, 3.9% to 5.1%).

Furthermore, patients with a prescription for OCSs might have had this prescription for a nonrespiratory diagnosis. However, because OCSs were always prescribed in combination with ICSs, we expect this group to be very small and not relevant to our results.

Finally, the proportion of patients with severe refractory asthma might have been overestimated because those patients

who had uncontrolled asthma because of continuous exposure to sensitizing agents at home or in the workplace[22] or because of untreated comorbidities (eg, rhinosinusitis and gastroesophageal reflux)[23] were included. In addition, it appeared that the nonresponders to the questionnaires were less adherent than the responders, which might have contributed to an overestimation of the prevalence of severe refractory asthma as well. On the other hand, there might have been an underestimation of the proportion of patients with severe refractory asthma because correction of undertreatment, poor adherence, and/or incorrect inhalation technique are no guarantee for good asthma control.[24,25] Thus some patients with difficult-to-control asthma might still have qualified as having severe refractory asthma after correction of these aggravating factors.

We can only speculate about the reasons for the difference between prevalences mentioned in the literature (5% to 10%) and our results (around 3.6%). Presumably, estimations in the literature are based on expert opinion and clinical experience. It is reasonable to believe that not all factors that negatively influence asthma control are receiving full attention in the consulting room. Therefore clinical overestimation of the prevalence of truly severe refractory asthma might easily occur because of misclassification of patients with difficult-to-control asthma as patients with severe refractory asthma.

Our results are important for clinicians because it is relevant to realize that the proportion of asthmatic patients with severe refractory asthma might be smaller than that of patients with severe asthma, as reported in the literature. This awareness stimulates us to thoroughly evaluate all potential aggravating factors in patients with uncontrolled asthma before considering treatment with systemic corticosteroids or expensive biological agents. Such an approach will obviously result in less undertreatment and overtreatment, lower health care costs, and less unnecessary side effects of treatment.

The results of the present study are also important for regulatory authorities involved in the development of new and targeted treatments for patients with severe refractory asthma. Because the prevalence of this condition might be lower than previously thought, severe refractory asthma could fulfill the criteria of a rare disease and qualifies for niche drugs. The US Food and Drug Administration and the European Medical Agency have set criteria according to which a disease is considered rare, and the development of novel medical treatments for these diseases is promoted by these agencies. The US Food and Drug Administration considers a disease rare if it affects fewer than 200,000 inhabitants in the United States (<6.3 per 10,000), and the European Medical Agency considers a disease rare if it has a prevalence of less than 5 patients per 10,000 inhabitants. According to our results, the prevalence of severe refractory asthma is around 10 per 10,000 adults. However, we know that within this category of patients, at least 3 distinct phenotypes exist, including severe early-onset allergic asthma, severe late-onset nonallergic eosinophilic asthma, and severe late-onset noneosinophilic asthma in obese female subjects.[26,27] This implies that each of these subphenotypes of severe refractory asthma might eventually fall under the category of rare disease.

In conclusion, our result show that 17.4% of asthmatic patients in a Western European country, such as The Netherlands, have difficult-to-control asthma, whereas a much smaller proportion, around 3.6%, fulfills the criteria of severe refractory asthma. Clinicians should be aware of the distinction between these 2 conditions and check potential aggravating factors, in particular poor adherence with treatment and inadequate inhalation technique. Assuming a prevalence of severe refractory asthma of 3.6%, subphenotypes of severe refractory asthma might qualify for rare disease. Hopefully, this revised labeling will facilitate the development and reimbursement of novel targeted treatments.

Clinical implications: Awareness of the prevalence of severe refractory asthma as opposed to difficult-to-control asthma can prevent undertreatment and overtreatment and result in lower health care costs and unnecessary side effects.

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