

Are the Asthma Guideline Goals Achieved in Daily Practice? A Population-Based Study on Treatment Adequacy and the Control of Asthma

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Key Words

Asthma epidemiology · Asthma control · Asthma severity classification · Drug therapy · Treatment appropriateness

Abstract

Background: The guidelines for asthma recommend that the use of anti-inflammatory therapy should be adapted to the severity of the disease. However, few data are available to assess the adequacy of the use of drugs and its influence on the control of asthma in 'real life'. **Methods:** The adequacy of the current use of anti-asthmatic medication according to the Global Initiative for Asthma (GINA) guidelines was assessed in a random sample of 400 asthmatics identified in the frame of the Italian Study on Asthma in Young Adults. Asthma severity was assessed using the GINA criteria; accordingly, a patient was classified as receiving inadequate treatment if his/

her current use of drugs was lower than that suggested by the guidelines for the corresponding severity level. The absence of asthma attacks in the last 3 months was used as an indicator of the disease control. **Results:** Fifty-five percent of the patients had persistent asthma. Overall, 48% (95% CI 41.2–54.8) of persistent asthmatics were receiving inadequate treatment, and 66% (95% CI 59.5–72.4) had not used their medication daily over the past 3 months. Persistent asthmatics who were inadequately treated had a significantly greater frequency of asthma attacks (geometric mean ratio 3.7; 95% CI 2.1–6.6) than those using an adequate dose of medication. Mild and moderate persistent asthmatics using an adequate medication regimen reported a low number of asthma attacks (median 0). At the multivariate analysis, a good control of the disease was positively associated with an adequate dose of anti-inflammatory medication (OR = 2.2; 95% CI 1.1–4.5) and was negatively associated with a later onset of asthma (OR = 0.96; 95% CI 0.93–0.99) and

severe asthma (OR = 0.37; 95% CI 0.17–0.81). **Conclusions:** Despite the increase in the use of inhaled corticosteroids, half of the persistent asthmatics from the general population are using a medication regimen below their severity level. When the use of drugs follows the GINA guideline recommendations, a good control of asthma is also achievable in the daily management of the disease, particularly in the case of mild and moderate asthmatics.

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Introduction

Under-treatment of asthma and particularly under-usage of inhaled corticosteroids (ICS) has been proposed as the reason for the insufficient control of asthma until the early 90s [1, 2]. Ten years ago, the Global Initiative for Asthma (GINA) guidelines were published and disseminated, emphasizing that the use of ICS should be the first-line therapy for all persistent asthmatics [3]. Since then, the use of ICS increased in many countries [4–6]. However, the most recent epidemiological surveys [7–9] suggest that the control of asthma is still poor in the general population, resulting in a heavy burden on society [10].

There are two possible reasons why the control of asthma falls far short of the goals of long-term management: (1) the treatment continues to be used inappropriately in relation to asthma severity, despite the availability of many effective drugs; (2) the goals set by the GINA guidelines may be over-ambitious for daily management.

An appropriate approach to therapy recommends that the type and dose of medications are increased with increasing asthma severity. The aim is to achieve control of the patient's asthma as quickly as possible. Once control is achieved and sustained for about 3 months, a reduction in therapy can be carefully considered in order to find the minimum therapy required to maintain control. An essential aspect of this approach is the need to monitor the effect of treatment (symptoms and lung function) and adapt the treatment to the severity of asthma [11].

For the patients already on treatment, the GINA guidelines suggest a classification of severity based on the clinical features present, as well as the daily medication regimen [11]. Given a certain degree of severity, the current treatment is adequate if it succeeds in reaching an acceptable level of control of symptoms. Progression to the next medication step is indicated when control is not achieved or is lost with the current treatment.

The management of this new approach to therapy in general practice and the proportion of asthmatics who are currently being treated according to GINA have up till now only been investigated in very few studies.

The aim of this study was to evaluate the appropriateness of the current use of asthma medication according to the GINA recommendations in a sample of Italian asthmatics from the general population and to assess the influence that an appropriate use of medication has on the frequency of asthma attacks. For this purpose, we planned a specifically designed study on asthmatics to collect quantitative information on daily use of medications, daily symptoms and asthma attacks. The most recent GINA severity classification approach was adopted.

Methods

Between 1998 and 2000, in the frame of the Italian Study on Asthma in Young Adults (ISAYA; for a list of participants, see appendix 1), a screening questionnaire investigating the presence of asthma symptoms and its management [7, 12] was sent to random samples of people aged 20–44 years in 9 Italian Centres (Pavia, Torino, Verona, Ferrara, Sassuolo, Pisa, Lucca, Livorno and Sassari). Overall, 15,591 out of 20,570 eligible subjects replied to the screening questionnaire (response rate 75.8%). Subjects were classified as current asthmatics if they reported a physician's diagnosis of asthma and had at least one asthma attack in the last 12 months and/or were under treatment at the time of the survey. Between April and June 2000, subjects with current asthma ($n = 527$) were invited to participate in a phone interview by trained health personnel aimed at collecting detailed information on symptoms and treatment. Four hundred subjects participated in this second stage of the survey (response rate 75.9%). The stages of the survey and their response rates are depicted in figure 1.

The phone interview lasted about 25 min and used a structured questionnaire that can be found at <http://biometria.univr.it/isaya/medication.doc>. Each subject had to report the frequency of symptoms over the past 3 months, qualitative information on their use of drugs over the last 12 months and quantitative information on the use of drugs over the past 3 months (type and brand of drug used, number of puffs per month if the subject used the drug when needed, number of courses, number of puffs per day and average number of days per course if the subject used the drug in short courses, and number of puffs per day if the subject used the drug continuously).

In agreement with the GINA guidelines to assess the severity of the disease in asthmatics already on treatment [11], the severity was based on a composite classification of the symptom frequency and the daily medication regimen the subject was on.

Symptom severity was classified in one of four steps according to the frequency of night-time and diurnal symptoms:

Step 4 (severe persistent): continuous night-time symptoms or continuous diurnal symptoms;

Step 3 (moderate persistent): night-time symptoms more than once a week or daily diurnal symptoms;

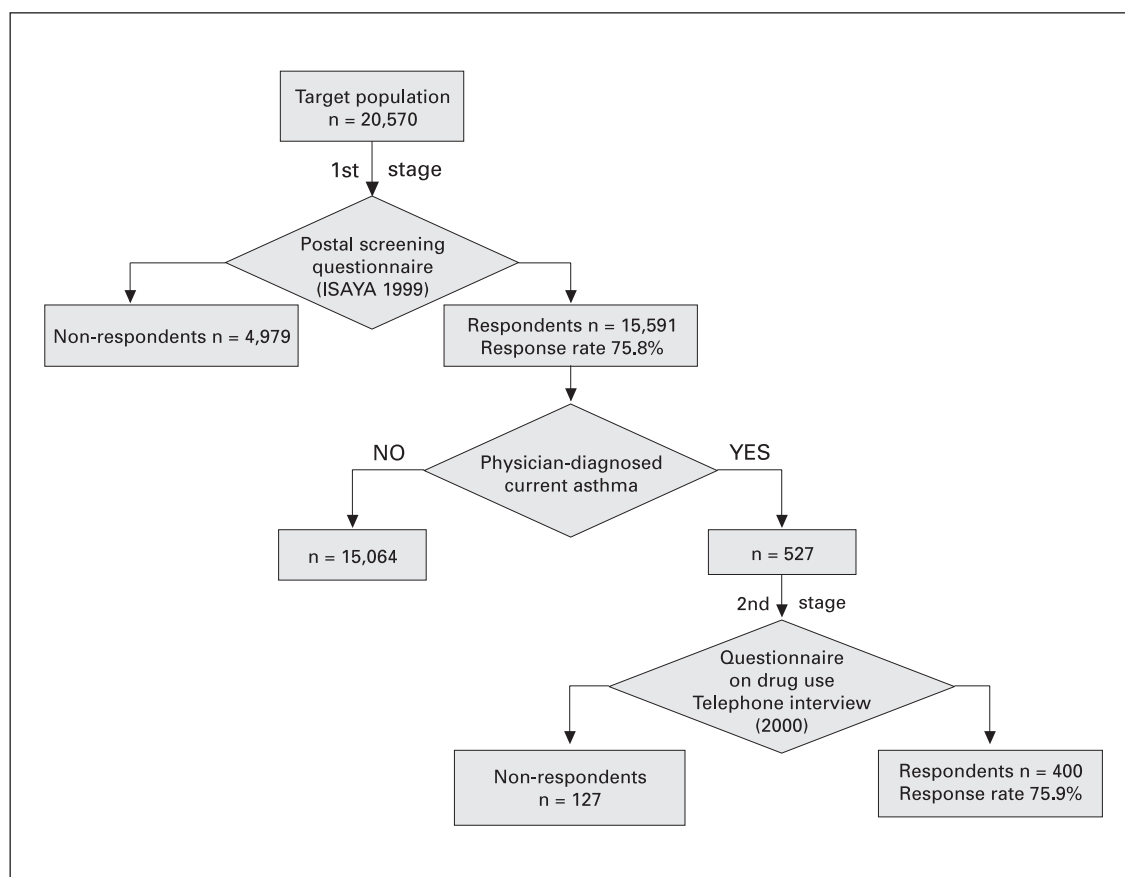


Fig. 1. Response rates to the different stages of the survey.

Step 2 (mild persistent): night-time symptoms more than twice a month or diurnal symptoms more than once a week and less than once a day;

Step 1 (intermittent): all asthmatics not satisfying the previous criteria.

Treatment was classified in one of four steps according to the average daily dose of ICS based on the last 3 months:

Step 4 ICS: beclomethasone dipropionate (BDP) >1,000 µg or an equipotent dose of other ICS or oral corticosteroids;

Step 3 ICS: 500 µg < BDP ≤ 1,000 µg or an equipotent dose of other ICS;

Step 2 ICS: BDP ≤ 500 µg or an equipotent dose of other ICS and/or theophylline and/or cromone and/or leukotriene modifiers;

Step 1: all other medications, including no treatment.

The equipotent doses of other ICS – budesonide, flunisolide, fluticasone and triamcinolone – were the ones reported in the GINA guidelines [11].

The final severity step of asthma was based on the two independent classifications of the symptoms and of the medication dosage according to GINA (fig. 2) [11]. An asthmatic could be classified as severe persistent either because of a very high frequency of symp-

toms or a high dosage of ICS, even if no symptoms were reported in the last 3 months.

According to GINA, the treatment was considered appropriate if it succeeded in reaching a low frequency of symptoms or if the medication dosage was the maximum available (fig. 2). Accordingly, by definition, all intermittent asthmatics were considered on appropriate treatment.

The presence of at least one attack of asthma and the average number of attacks in the last 3 months were based on the answer to the question ‘How many attacks of asthma have you had in the last 3 months?’ and were used as proxies for the control of asthma, which were independent of the severity classification.

Non-seasonal asthma was defined according to the answer to the question ‘Do you have asthma attacks every month of the year?’.

Subjects were classified as non-smokers, if they had not smoked at least one cigarette per day or one cigar a week for as long as 1 year, ex-smokers, if they had smoked for at least 1 year but not during the last month, and current smokers, if they had smoked for at least 1 year and also during the last month.

The duration of the disease was computed as the time (in years) between the first asthma attack and the patient’s age at the inter-

Fig. 2. Composite classification of asthma severity based on the frequency of asthmalike symptoms and on the medication classification according to GINA. Inappropriate treatment is indicated by underlined text. (See 'Methods' for a full description of the symptom and medication classification.)

		Frequency of symptom classification			
		Rarely	Occasionally	Frequently	Continuously
Medication classification	No ICS	Intermittent n = 180	<u>Mild persistent</u> n = 30	<u>Moderate persistent</u> n = 14	<u>Severe persistent</u> n = 7
	BDP ≤500 µg*	<u>Mild persistent</u> n = 66	<u>Moderate persistent</u> n = 23	<u>Severe persistent</u> n = 14	<u>Severe persistent</u> n = 11
	500 µg < BDP ≤1,000 µg	<u>Moderate persistent</u> n = 10	<u>Severe persistent</u> n = 1	<u>Severe persistent</u> n = 1	<u>Severe persistent</u> n = 4
	BDP >1,000 µg**	<u>Severe persistent</u> n = 20	<u>Severe persistent</u> n = 7	<u>Severe persistent</u> n = 6	<u>Severe persistent</u> n = 5

*BDP ≤500 µg and/or theophylline and/or cromone and/or leukotriene modifiers
**BDP >1,000 µg or oral corticosteroids

view. The compliance to treatment was defined as good, if subjects reported taking all of their prescribed medications, and poor, if subjects reported taking some or none of their prescribed medications [13].

Socio-economic status was classified according to the type of occupation: (1) managers, entrepreneurs, businessmen, clerks; (2) retired people, students and housewives; (3) unemployed, and (4) blue-collar workers. There were only 13 unemployed people, so they were aggregated to blue-collar workers.

The frequency of drug use in the 3 months prior to the interview was categorized as regular if a subject took them daily, non-regular otherwise. If a subject was using more than one drug, the frequency of drug use was determined by how often a subject used the ICS, if he/she was using them; if the subject was not using ICS, the regularity was determined by the frequency of the most intensively used medication.

To identify the factors associated with the control of the disease in persistent asthmatics, a logistic regression model was fitted to the data, using a dummy indicator (presence/absence of at least one asthma attack in the last 3 months) as the dependent variable and sex, age, age at onset, socio-economic status, smoking habits, severity, compliance, daily use of medication and adequacy of treatment as independent variables.

Comparisons of variables across strata were performed using the χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables.

The statistical analysis was performed using STATA software, release 7.0 (StataCorp, College Station, Tex., USA).

The protocol of the study was approved by the competent Italian Ethical Committee.

Results

The Sample

Out of 527 eligible asthmatics, 400 (75.9%) participated in the study. The difference between respondents and non-respondents was not statistically significant with respect to age, sex, duration of the disease, age at onset and reported symptoms. The mean age of respondents was 33.9 years (SD 7.3 years) and they had a long history of asthma, on average lasting for 18.4 years (SD 10.5 years). Sixty percent of current asthmatics reported having had diurnal symptoms, 30% nocturnal symptoms.

Asthma Severity

According to the GINA criteria, 180 (45.1%) subjects were classified as intermittent, 96 (24.1%) as mild persistent, 47 (11.8%) as moderate persistent, 76 (19.0%) as severe persistent asthmatics and one asthmatic was missing on severity (fig. 2, table 1). Daily symptoms (frequent/continuous) were reported by 48 (63.2%) of the severe persistent asthmatics and by 14 (29.8%) of the moderate persistent asthmatics (fig. 2). Intermittent asthmatics were equally distributed between men and women, whereas severe persistent asthmatics were mainly women, while mild and moderate persistent asthmatics were mainly men (table 1). There was no difference in age, age at onset and duration of the disease across severity steps. A high proportion of patients (33.8%) were current smokers, and

Table 1. Main characteristics of physician-diagnosed current asthmatics according to the asthma severity classification

	Intermittent (n = 180)	Mild persistent (n = 96)	Moderate persistent (n = 47)	Severe persistent (n = 76)	Total	p value
Women	51.7	43.8	42.6	68.4	51.9	0.0058
Age	33.5 ± 7.0	33.1 ± 7.2	34.7 ± 8.0	34.9 ± 7.5	33.9 ± 7.3	0.347
Age at onset	16.6 ± 11.5	14.2 ± 11.2	14.0 ± 10.5	16.3 ± 11.3	15.7 ± 11.3	0.253
Mean asthma duration	17.3 ± 10.7	18.7 ± 10.6	20.7 ± 10.0	18.7 ± 10.3	18.4 ± 10.5	0.244
Non-seasonal asthma	14.2	27.1	27.7	39.5	23.8	0.0002
Prevalence of diurnal symptoms in the last 3 months	28.9	74.0	87.2	94.7	59.2	<0.0001
Prevalence of nocturnal symptoms in the last 3 months	6.7	35.4	48.9	61.8	29.1	<0.0001
Smoking habits						0.771
Non-smokers	43.9	49.0	44.7	52.6	46.7	
Past smokers	19.4	17.7	25.5	18.4	19.5	
Current smokers	36.7	33.3	29.8	29.0	33.8	
Use of ICS in the last 3 months	0.0	54.2	68.1	67.1	33.8	<0.0001
Use of short-acting β_2 -agonists in the last 3 months	15.6	56.3	59.6	46.1	36.4	<0.0001
Use of long-acting β_2 -agonists in the last 3 months	1.7	9.4	14.9	34.2	11.3	<0.0001

Data are expressed as mean ± SD or percentage of patients.

this proportion was similar in all the severity categories. The prevalence of diurnal and nocturnal symptoms increased significantly in the more severe categories. In particular, severe asthmatics had a nine-fold higher prevalence of nocturnal symptoms than intermittent asthmatics (61.8 vs. 6.7%) and a three-fold higher prevalence of diurnal symptoms (94.7 vs. 28.9%). The prevalence of non-seasonal asthma increased significantly in the more severe categories.

Treatment Adequacy according to the GINA Guidelines

None of the intermittent asthmatics had used ICS (table 1), while the percentage of subjects using ICS in the last 3 months was 54.2, 68.1 and 67.1% in the mild, moderate and severe persistent asthmatics, respectively. The percentage of patients using short-acting β_2 -agonists showed a significant variation, ranging from 15.6% in the intermittent asthmatics to 59.6% in the moderate persistent asthmatics. The use of long-acting β_2 -agonists significantly increased with increasing severity ($p < 0.0001$).

Out of 219 persistent asthmatics (table 2), 51 (23.3%) received no treatment or used only β_2 -agonists or other bronchodilators (anticholinergics). Overall, 105 out of

219 persistent asthmatics (47.9%; 95% CI 41.2–54.8) were using inadequate treatment according to the GINA guidelines; the number of patients using a lower medication dose than that reported for their severity step was 30 (31.3%), 37 (78.7%) and 38 (50.0%) in the mild, moderate and severe persistent groups, respectively.

About 66% (95% CI 59.5–72.4) of the persistent asthmatics had not used medication daily in the last 3 months; the percentage of irregular users was 80.0, 66.0 and 49.4% in mild, moderate and severe asthmatics, respectively. Among persistent asthmatics with an appropriate anti-inflammatory dosage of ICS (52.1%), only 42.1% used them on a regular basis (daily use). The prevalence and the frequency of asthma attacks significantly increased with asthma severity ($p < 0.001$) (table 2).

Asthma Control

Asthma attacks were more common (70.2 vs. 49.1%; $p = 0.002$) and four times more frequent (geometric mean ratio 3.7; 95% CI 2.09–6.59) in persistent asthmatics with inadequate treatment than among adequately treated patients (fig. 3a, b). In particular, mild and moderate asthmatics with adequate treatment reported having had a low frequency of exacerbation in the last 3 months (the

Table 2. Treatment evaluation according to GINA severity steps

	Intermittent ^a (n = 180)	Persistent			All persistent (n = 219)
		mild (n = 96)	moderate (n = 47)	severe (n = 76)	
No medication or only β_2 -agonists ^b	180 (100)	30 (31.3)	14 (29.8)	7 (9.2)	51 (23.3)
Inadequate treatment ^b	0 (0)	30 (31.3)	37 (78.7)	38 (50.0)	105 (47.9)
Non-daily treatment ^b	172 (95.6)	76 (80.0)	31 (66.0)	38 (49.4)	145 (66.2)
At least one asthma attack ^b	36 (20.1)	49 (51.6)	27 (57.5)	53 (69.7)	129 (59.2)
Average number of asthma attacks, mean $\pm$ SD	0.6 $\pm$ 2.1	3.6 $\pm$ 12.0	6.0 $\pm$ 12.1	17 $\pm$ 29.4	8.8 $\pm$ 20.7
Average number of asthma attacks, median (interquartile range)	0 (0)	1 (3)	1 (5)	3 (15)	1 (5)

Data are expressed as number (percentage) of patients, unless otherwise indicated.

^a No medication and/or some medication have been considered appropriate for this severity step.

^b Percentage refers to the number of patients in a single severity step.

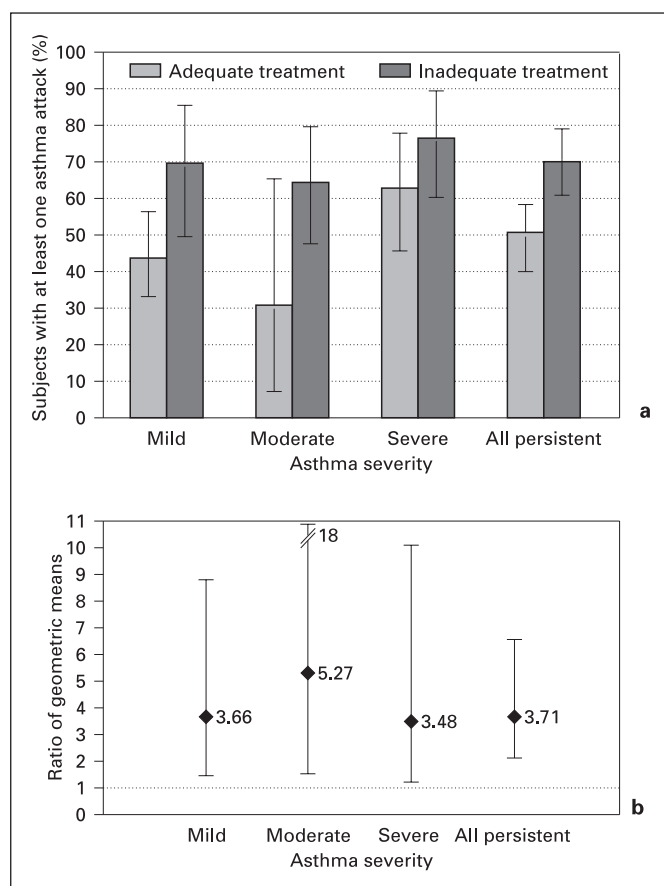


Fig. 3. **a** Percentage (and 95% CI) of subjects with at least one asthma attack in the last 3 months according to the adequacy of treatment and to asthma severity (persistent asthmatics). **b** Ratio (and 95% CI) of geometric means of the number of asthma attacks (inadequate/adequate) in the last 3 months according to asthma severity (persistent asthmatics).

median was 0 in both groups; the geometric mean was 0.41 for mild and 0.25 for moderate asthmatics).

The prevalence of asthma attacks was slightly lower in persistent asthmatics using daily treatment than in irregular users (52.7 vs. 62.1%; $p = 0.18$), while there was no difference in their frequency (median 1 vs. 2; geometric mean ratio 0.79; 95% CI 0.42–1.49).

Determinants of Asthma Control

Table 3 shows the mutually adjusted odds ratios for the association between the control of asthma (i.e. no asthma attacks in the last 3 months) and sex, age at onset, socioeconomic status, smoking habits, asthma severity, reported compliance, daily use of medication and adequacy of treatment in persistent asthmatics (adjusted by age). Persistent asthmatics with adequate therapy had more than a two-fold likelihood of not having exacerbation in comparison with non-adequately treated asthmatics, and a good control was inversely associated with severity. Daily use of treatment and self-reported compliance were positively associated with a good control, even if the association was not statistically significant. Furthermore, the probability of not having asthma attacks significantly decreased when the age at onset of asthma increased.

Discussion

This analysis was aimed at evaluating whether the use of drugs in asthmatics from the general population is adequate. For this purpose, we used the GINA approach according to which the treatment is adequate if, for a

Table 3. Determinants of asthma control

	Subjects n ^b	Subjects with a good control, %	Adjusted OR ^a (95% CI)	p value
Sex				
Men	105	45.7	1.0	
Women	114	42.1	0.93 (0.49–1.77)	0.831
Age at onset	–	–	0.96 (0.93–0.99)	0.005
Socio-economic status				
Manager, entrepreneur, businessman, clerk	117	42.7	1.0	
Retired person, student, housewife	58	51.7	1.51 (0.73–3.14)	0.269
Blue-collar worker and unemployed person	44	36.4	0.54 (0.23–1.26)	0.151
Smoking habits				
Non-smokers	108	47.2	1.0	
Past smokers	43	34.9	0.83 (0.36–1.92)	0.663
Current smokers	68	44.1	0.83 (0.41–1.66)	0.596
Asthma severity (persistent asthma)				
Mild	96	68.8	1.0	
Moderate	47	21.3	0.83 (0.35–1.98)	0.667
Severe	76	26.3	0.37 (0.17–0.81)	0.013
Self-reported compliance				
Poor	88	30.7	1.0	
Good	129	51.9	1.53 (0.79–2.95)	0.208
Daily use of medication				
No	145	38.6	1.0	
Yes	74	54.1	1.59 (0.79–3.20)	0.198
Adequacy of treatment				
No	104	29.8	1.0	
Yes	114	50.9	2.20 (1.09–4.47)	0.029

^a Adjusted for sex, age at onset, socio-economic status, smoking habits, severity, compliance, daily use of medication, adequacy and age.

^b n = 219; if the sums do not add up to 219, it is due to some missing data.

given severity step, it results in an acceptable control of symptoms (intermittent symptoms).

Our findings showed that half of the persistent asthmatics were taking anti-inflammatory drugs that were inadequate for their severity step and about 2 out of 3 of the subjects were not taking medication on a daily basis. Asthmatics that were adequately treated according to the GINA criteria had a better outcome than those without adequate treatment. In particular, adequately treated mild/moderate asthmatics reported a very low frequency of exacerbation, suggesting that, at least for these severity steps, the GINA goals can be reached when a proper management of the disease is performed.

To our knowledge, this is one of the first population-based studies that has tried to overcome the difficulties in classifying the severity of the disease in current asthmatics due to the confounding interrelations between severity, control and treatment. For this purpose, a detailed

quantitative measurement of medication use and daily symptoms was needed. Our treatment classification may be considered simplistic as it is mainly based on anti-inflammatory drugs, especially ICS; nevertheless, the guidelines recommend their use as a first-line therapy for the treatment of persistent asthma in adults, because they are the most effective controller drugs.

In contrast to the GINA guidelines, our classification did not include lung function measurements because these data were not available. This limitation could raise some concerns about the potential under-recognition of symptoms in patients with persistent disease. However, it has been shown that when the worst status of diurnal/nocturnal symptoms and medication step is used to categorize the patients, FEV₁ may only have a small effect on increasing the severity step [14, 15].

Although the clinical definition of control is much broader, in our analysis, we only took the frequency of

asthma attacks into consideration. However, no or a minimal number of asthma attacks are explicitly considered by GINA as one of the goals of the control, and the presence of asthma attacks is a predictor of hospitalization and a poor quality of life [16].

According to GINA, we evaluated the adequacy of the treatment and the achievement of the control of asthma only in persistent asthmatics, because, by definition, intermittent asthmatics only need symptomatic therapy. Our findings raise some doubts about this assumption; in fact, 20% of the intermittent asthmatics reported at least one asthma attack in the last 3 months. We are aware that it was not possible to investigate over-treatment with our composite classification of asthma severity, but we assumed that this problem only concerned a minority of patients with controlled persistent asthma. In fact, over-treatment could be a problem mainly for those subjects who rarely had symptoms (Step 1 of symptom severity) but were on treatment with large (medium or high) doses of inhaled corticosteroids (Steps 3 and 4 of medication classification). In our study, this mainly concerned 30 (10 moderate and 20 severe) out of 219 persistent asthmatics, i.e. 13.9%. However, the possibility to assess over-treatment requires information on the level of control reached in the last 6–7 months, not only in the last 3 months, and a longitudinal design. Both these features were not present in our study.

In agreement with other studies on the general population [17], we found that 55% of physician-diagnosed current asthmatics in Italy were persistent asthmatics.

According to the guideline, our results show that 48% of persistent asthmatics take a lower dosage of anti-inflammatory medication than they should, and 66% do not use their medication daily. Hence, the combination of these two findings shows that only 2 out of 10 Italian persistent asthmatics are getting the proper treatment daily. Inappropriate treatment is a major cause of poor clinical outcomes [18], social costs [19] and a poor quality of life [20]. Accordingly, probably as a consequence of an inadequate use of medication, we found that a large part of the Italian persistent asthmatics had a very high prevalence and frequency of exacerbation. The average number of asthma attacks reported in the last 3 months was more than three times higher in inadequately treated asthmatics than in adequately treated asthmatics. The association between an adequate dosage of medication and the frequency of exacerbation was particularly impressive in mild and moderate asthmatics, clearly showing that a good control of the disease can also be achieved in daily practice, at least for these severity levels.

It has been reported that the regular use of ICS and a good compliance is associated with a decreased risk of death and hospitalization owing to asthma [21, 22], as well as with fewer asthma attacks [23]. In our multivariate analysis, the regular use of medication and the self-reported compliance were positively associated with the absence of asthma attacks, even if the association was not statistically significant and the strength of the association was definitely lower than that related to an adequate dosage of anti-inflammatory drugs. However, it is worthwhile to note that the medication dosage has been computed as the average daily dose of anti-inflammatory drugs used in the last 3 months so that it could reflect, at least to some extent, both the regularity of use and the compliance to the treatment.

In agreement with previous reports [7], we found that a later onset of asthma and the severity of the disease are associated with a poor control of the disease. This supports the idea that asthmatics with a later onset of asthma must challenge a more serious form of the disease [12], which requires a great deal of effort for the management of the disease.

As expected, severe asthmatics reached a good control of the disease with more difficulty than mild/moderate persistent asthmatics, and this study highlights the fact that severe asthmatics experienced a considerable number of asthma attacks in the last 3 months, even if they followed the GINA guidelines. Nevertheless, adequately treated severe asthmatics reported a lower frequency of asthma attacks than non-adequately treated severe asthmatics (median 2 vs. 5.5, mean 9.5 vs. 24.4; $p = 0.01$).

In disagreement with other studies, we found no association between smoking habits and asthma severity [24, 25]. This could reflect either the young age of our subjects or a healthy smoker effect. Furthermore, our data show that the prevalence of current smoking in our sample of asthmatics is very high (33%), being almost identical to that of the rest of the population of the same age [26], pointing out that efforts made in smoking dissuasion among asthmatics have been inadequate.

Some caveats should be considered in the interpretation of our results because of the impossibility to assess the level of the control of asthma through objective measures. Instead, we based our findings on self-reported asthma attacks which may not reflect the actual degree of control. There are other indicators of asthma control, like diurnal and/or nocturnal symptoms. However, despite the fact that we had collected information on the frequency of diurnal/nocturnal symptoms, it was impossible to use the latter as an indicator of control because they were

part of the definition of severity (and also of adequate treatment). Instead, asthma attacks and the classification of severity as well as asthma attacks and inadequacy were completely independent and hence could be simultaneously studied.

In conclusion, our data show that 10 years after the publication and dissemination of the GINA guidelines and despite an increase in the consumption of ICS, their use is still inadequate. Five out of 10 persistent Italian asthmatics are using a medication regimen below their severity level and the inadequate dosage of anti-inflammatory drugs is the main predictor of the poor control of the disease. When properly treated, mild/moderate persistent asthmatics achieve a good control of the disease.

The reasons for the inadequate use of the medication may be treatment, clinician and/or patient related [27]. Our results clearly show the need for a better therapeutic cooperation between the physician and the patient for an improved management of the disease and a better quality of the asthmatic patient's life. In fact, as in the case of other chronic diseases, an adequate regimen and an optimal control can be reached by carefully monitoring the course of the disease, which demands the integration between clinical objective and subjective measures.

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Appendix 1

List of Principal Participants in the Italian Study on Asthma in Young Adults

Project leader: R. de Marco.

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References

- ▶ 1 Cerveri I, Zoia MC, Bugiani M, et al: Inadequate antiasthma drug use in the north of Italy. *Eur Respir J* 1997;10:2761–2765.
- ▶ 2 Janson C, Chinn S, Jarvis D, et al: Physician-diagnosed asthma and drug utilization in the European Community Respiratory Health Survey. *Eur Respir J* 1997;10:1795–1802.
- 3 National Institute of Health, National Heart, Lung and Blood Institute: Global initiative for asthma. NIH publication No 95-3659. Bethesda, Md., NIH, 1995.
- ▶ 4 Majeed A, Ferguson J, Field J: Prescribing of beta-2 agonists and inhaled steroids in England: trends between 1992 and 1998, and association with material deprivation, chronic illness and asthma mortality rates. *J Public Health Med* 1999;21:395–400.
- ▶ 5 Stafford RS, Ma J, Finkelstein SN, et al: National trends in asthma visits and asthma pharmacotherapy, 1978–2002. *J Allergy Clin Immunol* 2003;111:729–735.
- ▶ 6 Van Staa TP, Cooper C, Leufkens HG, et al: The use of inhaled corticosteroids in the United Kingdom and the Netherlands. *Respir Med* 2003;97:578–585.
- ▶ 7 de Marco R, Bugiani M, Cazzoletti L, et al: The control of asthma in Italy. A multicentre descriptive study on young adults with doctor diagnosed current asthma. *Allergy* 2003;58:221–228.
- ▶ 8 Rabe KF, Vermeire PA, Soriano JB, et al: Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. *Eur Respir J* 2000;16:802–807.
- ▶ 9 Vermeire PA, Rabe KF, Soriano JB, et al: Asthma control and differences in management practices across seven European countries. *Respir Med* 2002;96:142–149.
- ▶ 10 Fuhlbrigge AL, Adams RJ, Guilbert TW, et al: The burden of asthma in the United States: level and distribution are dependent on interpretation of the national asthma education and prevention program guidelines. *Am J Respir Crit Care Med* 2002;166:1044–1049.
- 11 National Heart Lung and Blood Institute: Global initiative for asthma. Global strategy for asthma management and prevention. NHLBI/WHO workshop report. NIH publication No 02-3659. Bethesda, Md., NIH, 2002.
- ▶ 12 de Marco R, Locatelli F, Cerveri I, et al: Incidence and remission of asthma: a retrospective study on the natural history of asthma in Italy. *J Allergy Clin Immunol* 2002;110:228–235.
- ▶ 13 Cerveri I, Locatelli F, Zoia MC, et al: International variations in asthma treatment compliance: the results of the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1999;14:288–294.

- ▶ 14 Colice GL, Burgt JV, Song J, et al: Categorizing asthma severity. *Am J Respir Crit Care Med* 1999;160:1962–1967.
- 15 Cazzoletti L: Asthma severity and treatment adequacy in ECRHS II (oral communication). Therapy and Health Economics Working Group, ECRHS II, Vienna, September 2003.
- ▶ 16 Foresi A, Paggiaro P: Inhaled corticosteroids and leukotriene modifiers in the acute treatment of asthma exacerbations. *Curr Opin Pulm Med* 2003;9:52–56.
- ▶ 17 Zureik M, Neukirch C, Leynaert B, et al: Sensitisation to airborne moulds and severity of asthma: cross sectional study from European Community respiratory health survey. *BMJ* 2002;325:411–414.
- ▶ 18 Shireman TI, Heaton PC, Gay WE, et al: Relationship between asthma drug therapy patterns and healthcare utilization. *Ann Pharmacother* 2002;36:557–564.
- ▶ 19 Anis AH, Lynd LD, Wang XH, et al: Double trouble: impact of inappropriate use of asthma medication on the use of health care resources. *CMAJ* 2001;164:625–631.
- ▶ 20 Bateman ED, Frith LF, Braunstein GL: Achieving guideline-based asthma control: does the patient benefit? *Eur Respir J* 2002;20:588–595.
- ▶ 21 Suissa S, Ernst P, Benayoun S, et al: Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000;343:332–336.
- ▶ 22 Suissa S, Ernst P, Kezouh A: Regular use of inhaled corticosteroids and the long term prevention of hospitalisation for asthma. *Thorax* 2002;57:880–884.
- ▶ 23 Dasgupta R, Guest JF: Factors affecting UK primary-care costs of managing patients with asthma over 5 years. *Pharmacoeconomics* 2003;21:357–369.
- ▶ 24 Siroux V, Pin I, Oryszczyn MP, Le Moual N, Kauffmann F: Relationships of active smoking to asthma and asthma severity in the EGEA study. Epidemiological study on the Genetics and Environment of Asthma. *Eur Respir J* 2000;15:470–477.
- ▶ 25 Althuis MD, Sexton M, Prybylski D: Cigarette smoking and asthma symptom severity among adult asthmatics. *J Asthma* 1999;36:257–264.
- ▶ 26 Cerveri I, Accordini S, Corsico A, Zoia MC, Carrozzi L, Cazzoletti L, Beccaria M, Marinoni A, Viegi G, de Marco R; ISAYA Study Group: Chronic cough and phlegm in young adults. *Eur Respir J* 2003;22:413–417.
- ▶ 27 Bender BG: Overcoming barriers to nonadherence in asthma treatment. *J Allergy Clin Immunol* 2002;109(suppl 6):S554–S559.