Control of asthma in real life: still a valuable goal?

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ABSTRACT Although studies show that control of asthma can be achieved in the majority of patients, surveys repeatedly show that this is not the case in real life. Important measures to implement in order to achieve asthma control are trained healthcare professionals, a good patient–doctor relationship, patient education, avoidance of exposure to triggers, personalised management and adherence to treatment. These measures help the majority of asthma patients but have not yet been widely implemented and there should be a concerted action for their implementation. Moreover, further and focused research is needed in severe/refractory asthma.

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Introduction

Asthma is a heterogeneous disease characterised by chronic airway inflammation. It is defined by a history of respiratory symptoms, such as wheeze, shortness of breath, chest tightness and cough, that vary over time and in intensity together with variable expiratory flow limitation [1]. Asthma prevalence has increased worldwide over the past decades [2] and it is estimated that it affects approximately 300 million people of all ages, races and geographic origins; it is believed that over 100 million more people will be affected by 2025 [3].

Previous Global Initiative for Asthma (GINA) guidelines were based on disease severity and classified asthma into four categories: mild intermittent, mild persistent, moderate persistent and severe persistent [1, 4]. However, several studies have shown that control of asthma is achievable in most patients regardless of the level of severity; for that reason, in recent years, asthma guidelines have distinguished asthma severity from asthma control [5]. Current recommendations are based on the level of asthma control rather than disease severity, and the role of the clinician is to establish the appropriate level of treatment

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for each patient in order to achieve control and then to adjust treatment in order to maintain control with the minimum but adequate level of therapy and minimum side-effects [1, 6].

The aim of the present review is to provide information on the importance of control-based asthma management in adult patients, and to describe the benefits and limitations of such an approach in everyday clinical practice.

Moving from asthma severity to control

Asthma severity is an inherent characteristic of the patient and it is defined by the frequency and severity of symptoms as well as the level of treatment that is required to control the symptoms or, in very severe asthma, by nonresponsiveness to treatment. Thus, asthma severity reflects simultaneously the activity of the underlying disease and the required level of treatment, and it may vary over time and in different asthma phenotypes [4].

Conversely, asthma control refers to the extent to which the manifestations of asthma have been reduced or eradicated by treatment [7]. Asthma control encompasses both the patient's symptoms and limitations (daytime symptoms, nocturnal symptoms, activity limitations and use of rescue medications) and the future risk of adverse asthma outcomes (including future exacerbations, development of fixed airflow obstruction and treatment-related adverse events) [1].

The clinical course of asthma can be extremely variable in the sense that both asthma severity and the level of control can change significantly over time. Thus, a patient with severe asthma can be well controlled and require no step up in treatment while a patient with mild asthma (usually requiring less intensive treatment) may have poor asthma control [8]. This mild asthma patient needs to be reviewed and their exposure to triggering factors, compliance to medication and level of treatment prescribed need to be assessed and adjusted to achieve control. Therefore, guidelines for the diagnosis and treatment of asthma are no longer focusing on disease classification according to disease severity but are mainly targeting disease control [1, 6].

The severity of asthma may represent a constant trait for a given patient and is related to the natural history of the disease; at present, there are no solid data showing major changes in disease severity in a longitudinal cohort. Conversely, this trait does not necessarily predict response to treatment. Therefore, control is easier to quantify and recognise, as both patients and healthcare providers can be taught to quantify changes in symptoms and lung function.

Defining asthma control

According to the current guidelines, asthma is defined as "controlled" if the patient reports symptoms and use of reliever medication less than twice a week, has no nocturnal symptoms, no activity limitation and has no important risk factors such as history of intubation, low forced expiratory volume in 1 s (FEV_1) or exacerbations in the last year. It is defined as "partly controlled" when daily symptoms and use of reliever medication are present more than twice a week and/or the patient experiences nocturnal symptoms and activity limitations, and as "uncontrolled" if three or more of the aforementioned conditions are present [1]. It is only recently that overall asthma control has been defined not only as the control of symptoms and functional limitations that the patient experiences as a result of asthma, but also as the minimisation of future risk of asthma exacerbations, prevention of lung function decline and prevention of medication side-effects [1, 7].

Defining asthma exacerbations

The American Thoracic Society (ATS) and the European Respiratory Society (ERS) set up a Task Force that reviewed the extensive literature on the definition of asthma exacerbations and defined severe asthma exacerbations as "events that require urgent action on the part of the patient and physician to prevent a serious outcome, such as hospitalisation or death from asthma" [4]. In this 2009 review, exacerbations were further graded into severe and moderate ("mild exacerbations" was not considered to be a useful term). The Task Force recommended that at least one of the following criteria should be used to define severe asthma exacerbations for clinical trials: 1) use of systemic corticosteroids (tablets, suspension or injection) or an increase from a stable maintenance dose, for at least 3 days; 2) hospitalisation or emergency department visit because of asthma, requiring systemic corticosteroids. The Task Force recommended the following criteria for the definition of moderate asthma exacerbations: 1) events outside the patient's usual range of day-to-day asthma variation; 2) deterioration in symptoms and/or lung function, and/or increased rescue bronchodilator use; 3) duration of 2 days or more, but not severe enough to warrant systemic corticosteroid use and/or hospitalisation.

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These definitions help in mild and moderate asthma but are less helpful in severe asthma, where day-to-day variability can be quite marked so it is more difficult to differentiate a moderate exacerbation from uncontrolled asthma. Severe exacerbations also occur in both mild and moderate asthma, and although they are less frequent than in severe asthma, they are quite common, as the mild/moderate state of asthma is much more prevalent than the severe.

Association of control with clinically important parameters

Asthma has an important impact in everyday life, not only because the patients may be significantly burdened by the symptoms of the disease (such as dyspnoea, cough and wheezing) but also because it leads to limitations in physical activities, sleep disturbance and negative effects in their work and social life, leading to anxiety and depression [9, 10].

Asthma control significantly affects the use of healthcare resources and the patients' quality of life, as assessed with the use of standardised health-related quality of life (HRQoL) questionnaires. Managing asthma effectively and achieving asthma control results in improvements in HRQoL and there is evidence that better asthma control is reflected in better HRQoL [11]. Moreover, asthma control deterioration is accompanied by deterioration of HRQoL [12]. Poor asthma control is also related to symptoms of depression, especially in patients with severe asthma, and it is believed that the presence of depression in these patients might have a negative impact on treatment adherence and HRQoL, leading to an ongoing vicious circle [9].

Risk factors for poor asthma control

Although clinical studies show that the majority of asthma patients can achieve control of their disease, several surveys have shown that in real life most asthmatic patients have poor asthma control [13, 14]. It seems that one of the main reasons for poor asthma control is the discrepancy between the perception of control by patients and the definition of control according to asthma guidelines [13]: asthmatic patients have low expectations regarding control of their asthma. A study among poorly controlled asthmatic patients in Canada has shown that up to 84% considered their asthma to be well controlled [15]. Furthermore, physicians often fail to recognise the level of asthma control in their patients and there is a lack of good communication between patients and doctors [16].

Causes of poor asthma control are multifactorial and are related either to the disease itself, to the physician or to the patient [17]. Factors related to the physician include asthma misdiagnosis, poor knowledge of current guidelines or difficulty in changing practicing routines, implementation of self-management plans in only a minority of patients and a poor doctor–patient relationship. The correct diagnosis is the first important step for the treatment of asthma, as missing the diagnosis will result in no treatment and no disease control and the differential diagnosis includes many other disease entities. Patients with other respiratory diseases misdiagnosed as asthma are unlikely to respond to asthma medication and, moreover, if treated in a control-based way, the lack of response will lead to progressively increased doses of medication, which will possibly result in notable side-effects without any benefit. Once diagnosis is established, assessment of severity and control is the cornerstone of asthma treatment because the doses of medication should be adequate to achieve control of the disease but should not be excessive, causing unwanted short- or long-term side-effects.

Physicians' knowledge of current guidelines has been proven to be weak. A study including general practitioners and specialists has shown that doctors lack important knowledge on asthma pathogenesis, control and treatment [18]. This is probably the reason why doctors have difficulties in changing their practicing routine and providing guideline-recommended control-based treatment of asthma. Finland has set an excellent example of how to train healthcare providers in asthma care. By educating its healthcare providers in a country-wide long-term programme, Finland managed asthma patients extremely well, cut down on emergency visits, inability pensions and lost work days and reduced overall asthma cost [19]. Thus, programmes at a national level are important.

Last but not least, a good doctor–patient partnership is one of the most important factors resulting in good asthma control [20]. Patients should be encouraged to express their needs and ask for information on their disease, and should be continuously educated on how to provide information about their levels of asthma control [20]. It is also very important that the doctor/healthcare provider has people skills and knows the patient's educational and cultural background, in order to provide information and guidance that can be understood and used by the patient.

Factors that are related to the patients include socioeconomic factors, adherence to medication, correct use of inhalers and patient expectations for disease improvement [17]. Patients often have inadequate knowledge about their asthma, are not able to recognise their symptoms, do not take their medication

correctly or try to reduce or stop treatment, and cannot identify signs of disease deterioration or monitor simple clinical parameters [21]. Studies have also shown that patients often overestimate their levels of control and that there is a discrepancy between self-perceived severity of asthma and objective assessment of severity [22]. The Asthma Control Test (ACT) includes a question about patient-reported level of control, and it has been suggested that the discordance between this question and the other four clinical fields could serve as a "red flag" for recognising patients who need to be further educated about their disease and the desirable level of control [23]. Incorrect use of inhalation devices is also very common and is associated with poor asthma control and adverse disease outcomes such as hospital admissions, visits to the emergency departments and courses of systemic corticosteroids [24]. Unfortunately, studies have shown that most healthcare professionals are not able to demonstrate correct inhaler technique and this results in further poor control of asthma [25].

Exposure to triggers, such as allergens, smoke, environmental and work-related irritants, as well as a sedentary lifestyle and poor diet, may be related to poor asthma control [26]. Avoidance of triggers is essential where possible, and this includes advice about allergen avoidance (house dust mites, pets, moulds) and change of work environment if necessary, while smoking cessation should be advocated at each visit. Other usual triggers, especially in adolescents and young adults, are cannabis and local toxins, which are related to wheezing, dyspnoea, nocturnal symptoms and severe asthma exacerbations requiring mechanical ventilation [27, 28]. Consultation and advice on when and how to step up treatment should be given for seasonal allergens or any increased exposure, as it is impossible to avoid being outdoors during a particular season or to live in a trigger-free environment. Other factors that might contribute to poor asthma control are continuous exposure to allergens and triggering factors, such as house dust mites, pets, occupational exposure and passive smoking, as well as the particular inflammatory profile of the disease (eosinophilic). Recognition and avoidance of these factors, where possible, is crucial for personalised management and adequate control [29].

Comorbidities, usually present in patients with asthma, are also a reason for poor disease control. The most common comorbidities that complicate asthma control are allergic rhinitis [30], gastro-oesophageal reflux disease (GORD) [31], obstructive sleep apnoea [32] and psychopathological comorbidities [33]. Allergic rhinitis often coexists with asthma and probably over 80% of patients with allergic asthma have concomitant rhinitis [30]. Asthma patients with severe rhinitis and rhinosinusitis seem to be four to five times more likely to have poorly controlled asthma compared with patients without rhinitis, while treatment of allergic rhinitis results in favourable outcomes regarding asthma control [34]. Numerous studies have shown that the respiratory lining is affected all along its length and rhinitis and asthma are expressions of the same disease spectrum [35, 36].

GORD is a common condition among asthmatic patients. In a recent report, 80% of asthmatic patients reported symptoms of GORD, while the use of pH monitoring identified GORD in 38% [37]. GORD is both a cause of poor asthma control and a risk factor for asthma exacerbations [38], although there is evidence that only symptomatic GORD influences asthma control [39]. Thus, treatment with proton pump inhibitors is not expected to improve poorly controlled asthma unless a patient suffers from symptomatic GORD [1, 40]. Obstructive sleep apnoea is another comorbidity that can be present in asthmatic patients and is related to increased asthma symptoms and poor asthma control [32]; sleep apnoea management with continuous positive airway pressure results in improvement of asthma control [41]. In a pivotal study from the Netherlands, factors significantly associated with frequent exacerbations included severe nasal sinus disease (adjusted odds ratio (OR) 3.7), gastro-oesophageal reflux (OR 4.9), recurrent respiratory infections (OR 6.9) and obstructive sleep apnoea (OR 3.4). However, the factor associated with the highest risk was psychological dysfunctioning (OR 10.8), and severe chronic sinus disease and psychological dysfunctioning were the only independently associated factors (adjusted OR 5.5 and 11.7, respectively) [31]. Risk factors for poor asthma control are summarised in table 1.

Assessment of asthma control

In everyday clinical practice, physicians assess asthma control based on the patient's report of daytime or nocturnal symptoms, the use of rescue medications, the limitations in everyday activity and the experience of previous exacerbations. However, when assessed in this way, asthma control seems to be overestimated and many patients, although uncontrolled, are misclassified as well controlled [42]. Moreover, when lung function measurements (such as spirometry and peak expiratory flow variability) are used, clinicians tend to overestimate the patients' improvement and underestimate their deterioration [43]. This highlights the need for validated tools for the assessment of asthma control. Two different types of tools may be used in order to monitor improvement or deterioration of asthma control. The first type is clinical and relatively simple and monitors symptoms through the use of standardised questionnaires, such as the ACT [23], the Asthma Control Questionnaire (ACQ) [44] and the Asthma Control Scoring System (ACSS) [45]. These questionnaires are simple and can be easily completed by the patient, and help the healthcare practitioner

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TABLE 1 Risk factors for poor asthma control

Factors	References
Disease-related	
Comorbidities: gastro-oesophageal reflux, obstructive sleep apnoea, psychiatric disease, allergic rhinitis and rhinosinusitis	[30–34]
Asthma type: aspirin sensitivity, neutrophilic activity, severe therapy resistant	[17]
Exposure to triggers: allergens, smoke, environmental and work-related irritants	[26]
Patient-related	
Low patient expectations regarding asthma control	[13, 17]
Poor patient perception of asthma control	[14, 21]
Low socioeconomic status	[17]
Poor adherence to medication	[17]
Incorrect use of inhaled medication	[17, 24]
Physician-related	
Absence of specialist care: inability of physicians to recognise poor asthma control, poor knowledge of current guidelines, misdiagnosis of asthma	[15, 17, 18]
Poor doctor–patient communication	[16]
No patient education on the correct use of inhaled medications	[24]
Rare implementation of self-management plans	[17]

to understand the level of asthma control and to recognise possible improvements or deteriorations. The second option involves the use of inflammatory biomarkers, usually in sputum or exhaled breath, that correlate to disease activity and may predict exacerbations and therefore provide information about the level of asthma control.

Clinical assessment questionnaires

The ACT is a simple questionnaire that consists of five simple questions with five possible response options (rated 1–5) for each. It includes questions about limitations of everyday activity due to asthma, the presence of daytime or nocturnal symptoms, the frequency of use of rescue medications and the personal perspective on the level of asthma control. Questions refer to the past 4 weeks and each answer is scored on a five-level scale (from 1 (worst) to 5 (best)). According to the sum of scores (5–25), asthma control is further categorised in three levels: uncontrolled (5–19 points), controlled (20–24 points) and optimally controlled (25 points). The minimal clinically important difference in this questionnaire has been shown to be a difference of 3 points [23].

The mini ACQ evaluates the level of asthma control in the previous week by asking the patient six questions regarding their symptoms (daytime and nocturnal symptoms, activity limitation, shortness of breath, wheeze and use of reliever medication) using a seven-point scale (from 0 to 6, with 0 representing no impairment and 6 representing maximum impairment). The scale exists in an extended version that also assesses the pre-bronchodilator FEV_1 on a similar seven-point scale. All scores are added and the final score ranges between 0 (well controlled) and 6 (extremely poorly controlled) [44].

The ACSS evaluates three types of parameters: the patient's symptoms (daytime symptoms, night-time waking due to asthma, activity limitations and use of rescue medications), pulmonary function (FEV_1 and/or peak expiratory flow variability) and, optionally, airway inflammation (eosinophilia in induced sputum). The first part is filled by the patient (according to the symptoms experienced during the preceding week), and the second and third parts are filled by the physician at the time of the assessment. Each part is quantified as a percentage and the total score is the mean percentage of the three parts, with 100% representing very well controlled asthma and 0% representing totally uncontrolled asthma [45].

Finally, the RAND Asthma Control Measure, a five-item self-reported asthma control survey measure, was shown to perform well in a large ethnically diverse sample of adults with asthma in the USA. It may provide a cost-free alternative to other asthma control measures currently available [46].

The ACT and ACQ are the questionnaires that are most extensively used in clinical practice, while the ACSS is mainly used in clinical studies. The ACT is available online in many languages.

Assessment using biomarkers

In recent years, research has focused on the use of biomarkers as a guide to treat asthma and achieve disease control. Symptoms are subjective estimations of the patients and often reflect their expectations,

whereas biomarkers have the advantage of being objective measurements of airway inflammation. In one of the first biomarker studies, sputum-guided treatment in addition to guideline-recommended monitoring was compared with symptom-guided treatment alone. It was shown that both strategies achieved similar levels of asthma control throughout the study, but the sputum-guided treatment group experienced fewer exacerbations [47]; this reduction in exacerbations was limited to eosinophilic exacerbations only, in a subsequent study with similar design [48]. Although very promising, this way of guiding treatment of asthma cannot be used in everyday clinical practice, as it is time consuming and requires special equipment and trained personnel and has a high cost. Therefore, it is only recommended for use in severe asthma monitoring and in specialised centres with experience, as stated in the recent ERS/ATS severe asthma guidelines [49].

The exhaled nitric oxide fraction (F_{ENO}) has also been used as a guide for the treatment of asthma in both children and adults [47, 50]. Although the use of this biomarker failed to show an overall benefit in clinical control or exacerbation rates, recent studies have shown that alterations in the levels of F_{ENO} are related to alterations in the level of asthma control and can predict exacerbations [51, 52]. This biomarker seems to effectively monitor asthma control, irrespective of confounding factors affecting its levels, including smoking [53] or concomitant allergic rhinitis [54]. Moreover, a double-blind study showed that the use of a validated F_{ENO}-based treatment algorithm can significantly reduce asthma exacerbations during pregnancy [55].

As F_{ENO} becomes more available in everyday clinical practice, especially with the use of portable and easy-to-use analysers, the use of this biomarker for the evaluation of asthma control and for the identification of control improvement or deterioration may represent a plausible option for the future.

Effects of treatment on asthma control

Results from randomised controlled trials

Control-based management of asthma in everyday clinical practice includes stepping up therapy when symptoms of asthma deteriorate and stepping down when control is achieved and sustained for a prolonged period of time [1]. It is important that control is sustained with of the lowest use of asthma medications. This is to ensure patient adherence to treatment, and to minimise side-effects and cost. Numerous randomised controlled trials have shown that asthma control is an achievable goal in a significant proportion of patients, when medications are used in rational and personalised way.

Studies in the late 1980s and early 1990s demonstrated the inflammatory nature of asthma and, since then, the generalised use of inhaled corticosteroids (ICS) even in milder disease has radically improved management of asthma and led to the reduction of symptoms and prevention of exacerbations [56]. The Formoterol and Corticosteroids Establishing Therapy (FACET) study was one of the first pivotal randomised controlled studies in asthma management and showed that the addition of long-acting β_2-agonists (LABA) (formoterol) to low or high ICS (budesonide) doses reduces the number of asthma exacerbations and leads to a lesser degree of inflammation [57]. Several years later, the Gaining Optimal Asthma Control (GOAL) study was another randomised study that compared the efficacy of fluticasone propionate *versus* salmeterol/fluticasone propionate combination in achieving total asthma control [58]. This study showed that the use of ICS alone achieves total control in above 50% of asthma patients and that the addition of LABA to any dose of ICS leads to the same result in a further 15–20% of patients. With total control as a target, a small percentage of patients, even mild ones, required oral steroids to achieve this goal and it has to be mentioned that 11–28% of patients did not achieve it even then. So it has to be argued whether total control is indeed the goal in asthma management. High ICS doses and more importantly oral corticosteroids are associated with side-effects and long-term risk and a more realistic goal should be targeting asthma management within safe long-term control. This translates into optimising treatment with the goal of minimal symptoms and limitations, and no exacerbations, but low long-term risk from high-dose medications. When control is not achieved with low-dose ICS, a LABA should be added to the treatments and several studies beyond FACET and GOAL have reported that asthma control is better achieved when a LABA is added to an ICS, compared with an increase in the dose of ICS [59, 60]. This is reflected in the current guidelines, which state that adding LABA reduces symptoms and exacerbations and increases FEV_1, while allowing a lower dose of ICS. The GINA guidelines add that, in at-risk patients, a low-dose ICS/formoterol maintenance and reliever regimen significantly reduces exacerbations, with a similar level of symptom control and lower ICS doses compared with other regimens [1]. However, even with the best strategies, a number of asthma patients, estimated at around 10–12%, require very high doses of medications to maintain control or fail to achieve control; these are the severe/refractory asthma patients. Guidelines for the diagnosis and management of these patients were recently published by an ERS/ATS Task Force [49]. Severe/refractory asthma requires not only follow-up in specialised centres but also much more research focusing on severe asthma mechanisms

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and phenotypes, as well as the cooperation of patients, doctors, researchers, the pharmaceutical industry and policy makers, in order to develop new effective medications and make them available to the patients who need them.

Results from surveys

Although it seems that asthma control can be achieved in the majority of patients participating in controlled trials, available data show that this is not the case in real life. In the Asthma Insights and Reality in Europe (AIRE) study, only a small percentage of patients fulfilled the criteria for controlled asthma while the majority of patients reported daytime and nocturnal symptoms as well as unscheduled healthcare visits [14]. Similar results have been also reported in other studies, in which patients reported night-time symptoms, absence from work or school and unscheduled emergency visits due to asthma exacerbations [61, 62], showing that asthma control among patients in real life is far from optimal [63]. Asthma control is not optimal even when patients are under specialist care and one important reason for this is non-adherence to treatment [64]. Patients try to reduce their treatment dosing and fear of side-effects is an important factor leading to noncompliance. Therefore, even patients with severe asthma use suboptimal anti-inflammatory medications [22, 62]. This is also often true during pregnancy, when fear of the medications' effects on the fetus leads many pregnant women to reduce or stop asthma treatment. It is important for both mother and fetus to adhere to optimal asthma treatment during pregnancy, as uncontrolled asthma may have significant perinatal morbidity and even mortality [65].

In conclusion, reasons for suboptimal asthma control in real life seem to be the presence of comorbidities, continuous exposure to irritants and importantly, inadequate adherence to treatment, more usually due to lack of education and a good patient–doctor relationship [66, 67].

Effects of asthma control on economic burden and healthcare cost

The annual cost of asthma largely depends on the level of control. The cost per uncontrolled asthma patient is more than twice as high as that of a patient with controlled asthma [68]. A previous study in Europe has shown that the cost of asthma therapy ranges from approximately €509 per year in controlled asthma to €2281 in patients with uncontrolled asthma [69]. Asthma control was the main determinant of the cost of persistent asthma [69]. Patients with poor asthma control require more hospitalisations, more visits to emergency departments and more use of healthcare services [17]. The financial burden related to uncontrolled asthma originates not only from the cost of medication and the use of healthcare services, but also from indirect costs, such as the loss of working days and the absence from non-work-related activities, which are significantly more prominent in patients with uncontrolled disease [68, 69].

Conclusion

Control of asthma symptoms and limitations as well as the minimisation of future risk, including exacerbations, fixed airway obstruction and side-effects, represent the central targets in asthma management, according to current asthma guidelines. The fact that we are not able to achieve adequate control in a significant proportion of our asthmatic patients, despite having medications and strategies that can be effective in most of them, stresses the importance of implementing effective asthma plans, based on evidence and the guidelines. The pursuit of normal or near-normal life, with minimal or no symptoms, minimal need for reliever medication and no impaired days and nights is an achievable goal. We do need to implement strategies for better definition of asthma control, as well as to identify means for the refinement of the communication of the meaning of asthma control and its elements between patients and doctors. Biomarkers may represent an option for the objective evaluation and implementation of control in asthma management, but this field needs further research. The biggest challenge we face is severe asthma, where even optimisation of treatment with the effective medications we have today does not achieve control of asthma and, therefore, focused research into the mechanisms of severe asthma and targeted new treatments is of high priority.

Control represents the optimal end-point of asthma management and deserves all our efforts to achieve it. It requires not only the efforts of healthcare professionals but also a good cooperation between doctors, patients, researchers, the pharmaceutical industry and policy makers, in an effort that will lead to better understanding of disease mechanisms and effective new medications, as well as good policies at country level, leading to prompt diagnosis, access to specialised healthcare and medications and effective management.

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