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Early View

Review

Asthma progression and mortality: The role of inhaled corticosteroids

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Title

Asthma progression and mortality: The role of inhaled corticosteroids

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Take-home message

There is compelling evidence of the value of ICS in improving asthma control, and indirect evidence that ICS prevent lung function decline by preventing severe exacerbations. Registry-based studies support the role of ICS in reducing asthma mortality.

Abstract

Overall, asthma mortality rates have declined dramatically in the last 30 years, due to improved diagnosis and to better treatment, particularly in the 1990s following the more widespread use of inhaled corticosteroids (ICS). The impact of ICS on other long-term outcomes, such as lung function decline, is less certain, in part because the factors associated with these outcomes are incompletely understood. The purpose of this review is to evaluate the effect of pharmacological interventions, particularly ICS, on asthma progression and mortality. Furthermore, the potential mechanisms of action of pharmacotherapy on asthma progression and mortality, the effects of ICS on long-term changes in lung function, and the role of ICS in various asthma phenotypes is reviewed.

Overall, there is compelling evidence of the value of ICS in improving asthma control, as measured by improved symptoms, pulmonary function and reduced exacerbations. There is, however, less convincing evidence that ICS prevent the decline in pulmonary function that occurs in some, although not all, patients with asthma. Severe exacerbations are associated with a more rapid decline in pulmonary function, and by reducing the risk of severe exacerbations, it is likely that ICS will, at least partially, prevent this decline. Studies using administrative databases also support an important role for ICS in reducing asthma mortality, but the fact that asthma mortality is, fortunately, an uncommon event, make it highly improbable that this will be demonstrated in prospective trials.

Introduction

Asthma deaths have been described from antiquity [1]. Henry Hyde Salter (himself suffering from asthma) wrote, in 1860, that the natural history of asthma is that while very young patients tend to recover and are at low risk of death, in those older than 45 years there is a progressive worsening of the disease increasing the risk of death [2].

Smoking [3] and chronic obstructive pulmonary disease (COPD) [4] are known to be associated with increased mortality, mainly due to non-respiratory causes. While there is no doubt that asthma deaths occur, and epidemics of asthma mortality have been reported in some countries from the 1950s through to the 1980s, likely caused by overuse of inhaled β_2-agonists [5], an unanswered question is whether patients whose asthma develops early in life have increased mortality risk due to asthma itself or other diseases. Reasons for this uncertainty include the heterogeneity of asthma, its frequent association with other diseases, and the poor accuracy of certified causes of death [6]. Some long-term studies, conducted in patients followed from asthma diagnosis, concluded that asthma itself, without concomitant risk factors such as smoking or reduced lung function, is not associated with reduced survival compared to age-matched controls [7–14]. In contrast, patients with late-onset asthma and elderly patients with asthma [15] appear to have increased mortality risk, particularly when associated with other diseases, mainly COPD (Figure 1), or reduced lung function [8–11, 13].

Overall, asthma mortality has declined in the last 30 years [16], due in part to improved diagnosis and more accurate certification of death, but also due to better treatment, particularly with the introduction of inhaled corticosteroids (ICS) [6]. However, no randomised clinical trial (RCT) has demonstrated improved survival as either a primary or secondary outcome in patients with asthma treated with ICS; the only evidence has come from registry-based studies [17, 18]. The purpose of this review is to evaluate the strength of the evidence of the effect of pharmacological interventions, particularly ICS, on asthma progression and mortality.

Natural history of asthma

Describing the natural history of asthma poses the same challenges as defining asthma. This is due to the heterogeneity of the airway diseases unified under the 'asthma' label [19]. Thus, the natural history may follow different paths of disease progression, including lung function decline, remission, reoccurrence, morbidity and mortality.

Information on asthma's natural history mainly comes from three types of studies. First, studies of patients with predominantly severe or difficult to treat asthma, conducted in specialised hospital clinics. Second, cohorts of individuals with asthma, both children and adults, enrolled in prospective population studies alongside healthy individuals. Third, registry-based studies using data retrieved from hospital, prescription and mortality records. Data from interventional studies can also contribute to knowledge of natural history, although such studies are usually too short to be extrapolated to a lifetime perspective. While studies from specialised departments often include well-characterised patients, they select a subgroup of individuals with the most severe asthma, representing less than 10% of the asthma population, who may have a much worse prognosis than the majority of individuals, with milder asthma, who use intermittent treatment and who have infrequent exacerbations [20]. General population cohort studies (and in particular registry-based studies) can be criticised for an uncertain diagnosis and poor characterisation of the participants, as they do not always include clinically important variables such as lung function, daily symptoms and biomarkers such as eosinophils or exhaled nitric oxide (FeNO). However, in recent years, a number of well-designed childhood asthma cohorts have cast new light on the progression of asthma from childhood to adolescence and even adulthood, with some of these cohorts including individuals who have reached their fifties [21].

Natural history of lung function in childhood asthma

Childhood studies suggest that at the time of diagnosis, as a group, children with asthma already have reduced forced expiratory volume in 1 second (FEV_1) and FEV_1/forced vital capacity (FVC) ratio. Longitudinal observations have identified several trajectories that

differ from normal, in terms of maximal FEV_1, the duration of the FEV_1 plateau during early adulthood, and the age at onset of FEV_1 decline. In one study, only 25% of children had a normal pattern of lung function development, whereas 26% had reduced growth and an early decline, 23% had reduced growth only, and 26% had normal growth and an early decline [22].

In another cohort, children with the most severe symptoms had reduced lung function both at the age of 10 years and when they reached their fifties. However, lung function decline (FEV_1 and FEV_1/FVC ratio) between 20 and 50 years of age was no faster than in the control group without asthma, and was not related to initial asthma severity [23]. A similar pattern was observed in still another cohort, where children were followed from the age of 10–15 to 60–65 years [24]. Thus, it seems that childhood asthma mostly exerts its deleterious impact on lung function during the growth phase [25]. Factors that predict suboptimal development resulting in poorer lung function in adulthood include low baseline FEV_1, severe and persistent symptoms, early sensitisation, lower bronchodilator response, airway hyperresponsiveness (AHR), and male sex.

The effect of active smoking on lung function in individuals with childhood asthma and early onset asthma has been a subject of debate [26–28]. Some studies suggest that the role of smoking with regard to driving lung function impairment is small in this group [29]. Other studies suggest that smoking only plays an important role in those with non-atopic asthma [30], whereas still other studies suggest a synergistic effect of atopy and smoking resulting in chronic airflow limitation [31].

Natural history of lung function in adult-onset asthma

Most studies in adults show that, as a group, individuals with asthma have a lower FEV_1 and FEV_1/FVC ratio than healthy individuals. Predictors of reduced lung function include adult-onset, long-standing disease, severe symptoms, frequent exacerbations, smoking, ongoing exposure to allergens and occupational agents, chronic mucus

hypersecretion, and high levels of AHR, IgE and eosinophils [26]. Some of these predictors have been reproduced in longitudinal studies, where the outcome has been lung function decline. The initial focus of these analyses was whether lung function declines faster in asthma than in healthy individuals, including the role of smoking [32, 33]. More recent longitudinal studies identified potentially modifiable characteristics related to faster FEV_1 decline, including high frequency and severity of exacerbations [34, 35], and elevated FeNO and eosinophils [36–38].

Earlier studies did not differentiate between childhood-onset versus adult-onset asthma [39]. This is relevant, as adult-onset asthma, in addition to a poorer response to therapy, seems to be associated with a higher risk of disease progression, including faster FEV_1 decline [40–42]. Furthermore, the presence of airflow limitation at baseline in individuals with asthma, a condition sometimes labelled asthma-COPD overlap (ACO), is also associated with faster FEV_1 decline, in particular in those with onset of asthma after the age of 40 years [13]. In contrast, both early-onset asthma without airflow limitation at baseline and ACO with early-onset asthma are associated with subsequent normal FEV_1 decline [13].

Mortality in asthma

Most deaths from asthma are preventable. While asthma mortality has reduced substantially over the last few decades in most countries, asthma deaths still occur, and are strongly related to social deprivation, even in developed countries [43, 44]. This suggests poor access to healthcare and medications and low adherence to ICS are important modifiable factors. In addition, studies from both before and after the introduction of ICS suggest that the overuse of potent inhaled β_2-agonists increases asthma mortality [5].

Patient characteristics related to increased risk of death in asthma include similar factors to those related to rapid lung function decline. Thus, severe and difficult to treat asthma, late-onset asthma, current smoking, presence of chronic airflow limitation,

eosinophilia, bronchial hypersecretion, AHR , aspirin sensitivity, previous intensive care unit admissions, and the presence of heart disease has been related to poorer survival [7, 45–48]. Recently it has become clear that individuals with characteristics of both asthma and COPD (ACO) have reduced survival. In the Copenhagen City Heart Study, life expectancy compared to healthy never-smokers was reduced by approximately nine years in those with ACO and early-onset asthma, and by 13 years in those with ACO and late-onset asthma, whereas it was only reduced by three years in individuals with asthma, preserved lung function and low tobacco exposure [13] (Figure 2). In a Danish cohort, women with ACO showed higher mortality compared to those with asthma or COPD alone [49].

Earlier epidemiological studies, based on longitudinally followed cohorts or on health registries, have consistently shown that individuals with asthma from the general community, as a group, have a higher risk of death than healthy individuals, with a hazard ratio of 1.5 [46, 50]. The increased risk is caused by higher mortality from respiratory diseases, including COPD, and pneumonia. It has also been debated whether asthma, like COPD, also predisposes individuals to a higher risk of developing ischaemic heart disease and lung cancer. However, a study focusing on long-term prognosis of smokers and never-smokers with asthma suggests that these associations may have been caused by inadequate adjustment for smoking, social status, and, in the case of heart disease, cardiovascular risk factors [14, 51].

Changing concepts in asthma diagnosis, severity assessment and treatment, and their effects on asthma progression and mortality

The first guidelines on asthma diagnosis and management were published in the late 1980s [52–55]. The development of these documents was stimulated by an increase in asthma-related mortality in several countries (particularly New Zealand [5]) and a marked increase in asthma prevalence in many countries in the 1970s and 1980s [56]. These were consensus statements, rather than formal evidence-based clinical practice guidelines, but all

identified the need to establish the diagnosis of asthma using objective criteria to document variable lung function, which has not changed over time, and recommended treatment options based on the perceived severity of the disease. The objectives of treatment were to improve symptom control and lung function. The importance of airway inflammation in asthma pathogenesis had already been identified [57], but the early documents did not emphasise the benefits of anti-inflammatory treatments, and as a result medications that rapidly improved symptoms and lung function, particularly inhaled β_2-agonists, were the focus of treatment, particularly for patients with mild-to-moderate asthma.

The effects of an over-reliance on inhaled β_2-agonists were profound [58]. The most commonly used are short-acting inhaled β_2-agonists (SABAs), which with regular use as the only treatment for asthma are now known to promote eosinophilic airway inflammation [59], cause a deterioration of asthma control [60], and in some instances increase the risk of asthma mortality [61]. The increase in asthma mortality risk is also seen when long-acting inhaled β_2-agonists (LABAs) are used as the only treatment [62].

A paradigm change in asthma management has occurred, in that management now focuses on overall asthma control, consisting of two domains: achieving current asthma control, and minimising future risk, particularly of severe exacerbations, but also of loss of lung function, and side effects of medications. Asthma severity is now defined by the level of treatment needed to control the disease [63], rather than, as previously, a complex algorithm of symptoms, lung function and reliever use, which did not take treatment requirements into consideration. In addition, there is an improved understanding of the role of airway inflammation in causing the manifestations of asthma, including symptoms, variable airflow obstruction and severe exacerbations. Indeed, severe exacerbations have not only been recognised as a vitally important target for treatment, but are also associated with progression of asthma and a more rapid decline in lung function [35].

These changes resulted in an enhanced appreciation of the pivotal role for ICS in asthma management. ICS treatment is known to improve all manifestations of asthma and to

reduce asthma mortality [17], and over the past decade maintenance ICS treatment has been recommended for all patients with symptoms requiring reliever use two or more times per week. More recently, because of an increased understanding that patients considered to have mild asthma have greater morbidity than previously appreciated [64], ICS are now recommended as a treatment option for all patients [6]. Also, the use of ICS/rapid onset β_2-agonists as a reliever medication for all patients with asthma, in preference to SABA alone, has been another very recent addition to treatment recommendations (Figure 3) [65].

A result of this focus on ICS use, either as monotherapy for mild asthma or together with LABA in a single inhaler for patients with moderate to severe disease, is that the risks of severe asthma exacerbations and associated emergency room visits or hospitalisation have declined, both in clinical trials where these treatment options have been studied [66–68], and in real-world settings. A study from Ontario, Canada, reported an almost 50% reduction in emergency room visits for asthma between 2003 and 2013 [69], with overall asthma mortality decreasing in countries where this has been measured [43, 70].

Effect of current medications on severe asthma progression and mortality

Most patients can achieve satisfactory control of their asthma from an ICS with or without a LABA. However, 5–10% have severe disease, requiring extensive treatment to achieve control or remaining uncontrolled despite such treatment [71, 72]. This subgroup accounts for the majority of morbidity and mortality due to asthma, and for 60% of the total healthcare costs attributable to asthma. Furthermore, patients with a recent history of an asthma exacerbation have particularly high annual healthcare costs, estimated to be three times those of patients with severe asthma and no history of an exacerbation [73].

Severe asthma is heterogeneous with respect to the clinical problem, nature of lung function impairment, and underlying pathology [74]. It is often complex, as many patients have a clinically severe condition primarily because the diagnosis is incorrect, or due to

issues with inhaler technique or treatment adherence. Other patients have persistent asthma-like symptoms primarily driven by comorbid factors. The international European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines on severe asthma acknowledge these difficulties and have produced the most widely accepted definition [71]. This is “asthma which requires treatment with guidelines suggested medications for GINA Stages 4–5 asthma (high dose inhaled corticosteroid and LABA or leukotriene modifier/theophylline) for the previous year or systemic corticosteroid for ≥50% of the previous year to prevent it from becoming ‘uncontrolled’ or which remains ‘uncontrolled’ despite this therapy”. The diagnosis of asthma should be confirmed and comorbidities addressed before making a diagnosis of severe asthma.

An important aspect of the ERS/ATS definition is that different criteria for uncontrolled asthma are identified, and no assumptions are made about the involvement of pathophysiological pathways. This is important as it is increasingly clear that different mechanisms drive different aspects of the clinical problem [74]. For example, symptoms likely reflect airway dysfunction, comorbidities and psychological factors more closely than underlying type-2 high airway inflammation, whereas severe exacerbations more closely reflect bronchodilator unresponsive airflow limitation due to eosinophilic, type-2 high airway inflammation. The mechanisms driving progressive loss of lung function are less clear, but neutrophilic and type-2 high airway inflammation may be contributory [36, 75]. Therapeutic interventions also impact clinical problems differently, with LABAs having a proportionately bigger impact on symptoms and lung function than exacerbations (particularly more severe events), whereas the opposite is true for ICS or a step-up in ICS dose [76].

The high level of morbidity, healthcare costs and treatment-related side effects in severe asthma mean that there is large unmet need for alternative therapies. Treatment should target the pathophysiological mechanism responsible for the clinical problem and should be adapted for each individual patient. One particularly fruitful area of development has been the use of monoclonal antibodies targeting type-2 cytokines involved in the

development of type-2 high airway inflammation [72]. These treatments have a large impact on exacerbation frequency but a less impressive effect on symptoms and lung function. The first of these, anti-IgE (omalizumab), is now known to be particularly effective in patients with evidence of type-2 airway inflammation [77]. A number of newer approaches including anti-IL-5 (mepolizumab, reslizumab), anti-IL-5 receptor (benralizumab) and anti-IL-4Rα (dupilumab which blocks IL-4 and IL-13), have been approved by regulatory authorities for treatment of severe eosinophilic asthma.

A recent large epidemiological study has shown that most patients with severe asthma transition to less severe disease over time [78]. Low socioeconomic class, comorbidity and high medication use were all identified as predictors of remaining severe. Clinical trials of biologic agents in severe asthma (Table 1 [79–86]) have shown that symptoms improve markedly with placebo treatment within the first month or so, but little thereafter. The effect of biological treatment on top of this is modest, implying that non-inflammation related factors, such as comorbidities, are driving many residual symptoms. The findings of high correlation between the presence of obesity and a high Hospital Anxiety and Depression Score and reported symptoms in severe asthma [87] are also consistent with this.

Less is known about changes in lung function over time, and analyses are complicated by the inherent variability of lung function in asthma, large placebo effects in many studies, and limited follow-up duration. As a result, definitive conclusions about the rate of decline in lung function in severe asthma and the impact of treatment are not possible. Nevertheless, the very large populations studied and the use of novel methods to assess airway structure, allow some tentative conclusions. Haldar et al [88] reported a reduction in computed tomography assessed bronchial wall thickening after one year's treatment with mepolizumab suggesting some effect on airway remodelling. In keeping with this, Castro et al [86] found a statistically significant difference in the rate of decline in post-

bronchodilator FEV_1 in patients with moderate to severe asthma after one year with dupilumab.

Exacerbations requiring oral corticosteroid treatment, or resulting in emergency department visits and/or hospitalisation occur more frequently in severe asthma, and are generally much more responsive to treatment with biological agents than other outcome measures (Table 1). Risk factors for these events include poor treatment adherence, low lung function and particularly a prior history of exacerbations [72]. In addition, clinical trials have shown a consistent relationship between an increased risk of exacerbations and a raised blood eosinophil count or FeNO [89]. These biomarkers are also predictive of efficacy of biological treatment, with blood eosinophils relating most closely to the response to anti-IL5 [90] and FeNO to the response to anti-IL4/13 [86] and omalizumab [77].

The morbidity associated with regular [91] or frequent rescue oral corticosteroid use, such as weight gain, diabetes mellitus, hypertension, osteoporosis and cataract formation [92], is considerable and impacts most on patients with severe asthma. Biological agents have marked oral corticosteroid sparing effects [93–95] so it is likely that this is another aspect of the longer-term natural history of severe asthma that will be improved in future.

Table 1. Summary of the effect of treatment on pre-bronchodilator FEV_1, asthma exacerbations and mortality. Events are expressed as episodes/patient/year unless otherwise specified. Asthma severity based on treatment requirements and prior asthma exacerbation rates. Ranges indicate results with different doses/routes of administration.

Study	Number	Duration	Asthma severity	Treatment group	Change from baseline in pre-bronchodilator FEV_1	Exacerbations		Mortality (%)[†]
						Overall	ED and hospitalisation	
Busse et al [79]	36,010	26 weeks	Moderate	ICS	Not reported	11.7%	0.60%	0
				ICS/LABA	Not reported	9.8%	0.66%	0
DREAM [80]	616	52 weeks	Severe	Placebo	60 mL	2.40	0.43	0
				Mepolizumab	115–140 mL	1.15–1.46	0.17–0.25	1
MENSA [81]	576	32 weeks	Severe	Placebo	86 mL	1.74	0.20	1
				Mepolizumab	183–186 mL	0.83–0.93	0.08–0.14	0
MUSCA [82]	551	24 weeks	Severe	Placebo	56 mL	1.21	0.10	0
				Mepolizumab	176 mL	0.51	0.03	0
CALIMA [83]	1306	56 weeks	Severe	Placebo	215 mL*	0.93*	0.04*	0
				Benralizumab	330–340 mL*	0.60–0.66*	0.04–0.05*	0
SCIROCCO [84]	1205	48 weeks	Severe	Placebo	239 mL*	1.33*	0.18*	0
				Benralizumab	345–398 mL*	0.65–0.73*	0.06–0.11*	0
Castro et al [85]	953	52 weeks	Severe	Placebo	120 mL	1.81	0.12	0
				Reslizumab	220 mL	0.84	0.077	0
QUEST [86]	1902	52 weeks	Moderate-severe	Placebo	180–210 mL[‡]	0.87–0.97	0.065	0
				Dupilumab	320–340 mL[‡]	0.46–0.52	0.035	0

ICS, inhaled corticosteroid; LABA, long acting β_2-agonist; FEV_1, forced expiratory volume in 1 second; ED, emergency department.*Data are for the subgroup with severe asthma and eosinophils ≥300 cells/µL (n=728 in CALIMA and 809 in SCIROCCO). †Rounded to 0 decimal places. FEV_1 data are change from baseline at the final study visit, with the exception of ‡ which are change from baseline at Week 12.

Effects of current medications on mortality

As previously discussed, the decreases in asthma mortality in the last 30 years are a result of improvements in socio-economic conditions and of pharmacological treatment [6, 96]. The latter can be briefly summarised as the identification of the overuse of rescue SABA and no controller medications (ICS) as a risk factor for asthma death [61], the increasing use of ICS [17], the superiority of ICS/bronchodilator combinations in controlling moderate and severe asthma [76, 97], the introduction of combined ICS and fast-acting β_2-agonists (i.e., formoterol) as both reliever and controller medication [68, 98], the additional effect of tiotropium [99], and the introduction of monoclonal antibodies in severe asthma [100].

The optimisation of care that takes place when patients are enrolled in controlled clinical trials must be taken into account when evaluating evidence provided by RCTs, including severe adverse events and hospitalisations and death. Clearly, adherence to care in these settings is profoundly different from that in real life.

A report on asthma deaths published by the UK College of Physicians underlines that the strongest risk factors for asthma death are over-use of β_2-agonists, absence of maintenance anti-inflammatory treatment, previous hospitalisation, and poor adherence to guideline recommendations [101]. The suggestions provided for preventing asthma deaths can be summarised in the concept that every hospital and primary care practice should have designated specifically labelled clinical services, responsible for formal training in the identification of the patients at risk of asthma death and proper management of acute asthma [101]. This is particularly relevant considering that more than 95% of asthma deaths occur in adults with identifiable risk factors, and that more than 85% of asthma deaths occur not acutely, but as progressive worsening. Data from the Finnish Asthma Programme confirm that the introduction of anti-inflammatory treatment (principally ICS) was associated with a decline in asthma morbidity, thereby reducing the utilisation of emergency services, hospitalisations and deaths [102]. Given this background, it is difficult to explore the mechanisms of action of currently available medications in terms of prevention of asthma

mortality. Further, it is impossible to conduct RCTs to test treatment efficacy or mechanisms on such an outcome due to the extremely small number of events.

Currently available biologic treatments are effective in reducing exacerbations, hospitalisations and near fatal adverse events, and it is possible that they may prevent acute fatal events. Real life observations will provide this information in the future. However, all presently available agents, including approved biologicals and new chemical entities in development, are believed to work predominantly in patients with type-2 high disease [100]. Unfortunately, nothing new appears to be available for patients with severe type-2 low asthma [71, 96, 100].

Impact of ICS on long-term changes in lung function

In the majority of individuals with asthma, treatment with ICS improves symptoms and lung function, reduces the frequency of exacerbations and reduces airway inflammation [6]. In addition, the very earliest studies of the efficacy of ICS in asthma demonstrated their ability to reduce or eliminate the need for oral corticosteroids as a maintenance treatment [103, 104]. Furthermore, registry studies have shown that even low doses of ICS reduce the risk of severe asthma exacerbations and death from asthma [17, 105]. The ability of ICS to reduce the risk of severe exacerbations can even be seen when ICS and rapid-onset inhaled β_2-agonists, delivered from the same inhaler, are only used as a reliever treatment [66, 106].

It has been much more difficult to prove whether long-term ICS treatment leads to a better outcome with regard to preservation of lung function. As mentioned earlier, a substantial minority of patients with asthma experience accelerated decline in FEV_1 and FEV_1/FVC, potentially leading to irreversible airflow limitation [107]. This is likely to be caused by airway wall thickening, so called airway remodelling, rather than development of emphysema as in COPD [108]. Studies suggest that some components of airway remodelling may be reduced by ICS [109, 110]. Since ICS, particularly in combination with LABAs, can reduce the risk of severe asthma exacerbations that may accelerate FEV_1

decline, early initiation of long-term treatment may alter the natural history of FEV_1 decline in the subgroup of patients who are prone to rapid loss of lung function [111].

Observational, non-randomised studies of both children and adults followed in asthma clinics [112, 113] and studies of adults with asthma from the general population [114] have suggested that ICS treatment may have beneficial effects on the course of lung function. However, this has been very difficult to prove in a RCT, since in excess of three years of observation are needed to draw conclusions about long-term changes in FEV_1, due to the combination of considerable measurement error and a very modest age-related annual FEV_1 decline [115]. In addition, randomisation of individuals with even mild asthma to placebo maintenance therapy may result in substantial withdrawal during such a study due to inadequately controlled symptoms and the occurrence of exacerbations.

However, two RCTs with sufficiently long observation periods have evaluated the effect of ICS on longitudinal lung function changes. The CAMP study randomised children older than five years of age with mild-to-moderate asthma to budesonide, nedocromil or placebo and followed them for up to six years [116]. The study found no benefit of ICS over either nedocromil or placebo regarding the growth velocity in post-bronchodilator FEV_1. The START study randomised children and adults with mild persistent asthma of less than two years duration to either budesonide or placebo as maintenance medication [117]. There was a reduced mean decline from baseline in post-bronchodilator FEV_1 at one and three years in the budesonide group compared with placebo, both in adult smokers and non-smokers [118]. After three years, all patients were given budesonide; those switched from placebo to budesonide caught up to those who received budesonide throughout the study in terms of several clinical variables, including FEV_1 [119]. This result on lung function is similar to that seen in the CAMP study.

Another study of early intervention with ICS showed clear benefits in the group who initiated ICS early compared to those initially treated with SABA as needed, including a better improvement of lung function [120]. After the initial two years of, the participants who

initially started on SABA were switched to ICS. On conclusion of the study, participants had their ICS dose adjusted in a real-life setting. After 13 years of follow up, the investigators could no longer observe differences with regard to lung function in those initiating the ICS therapy early versus those who started ICS after two years [121].

Role of ICS, alone or in combination, in different asthma phenotypes

The understanding of the biology and pathophysiology of asthma has progressed, with the identification of a number of distinct phenotypes [87, 122, 123]. However, current international guidelines recommend initiating ICS treatment to almost all patients [6]. ICS work through both positive gene regulation and gene repression, with the result of this dual action being potent anti-inflammatory action in the airways [124].

The improvement with ICS in some clinical parameters, such as spirometry, is variable [125]. As a result, different biomarkers, alone or in combination, are being used to increase the predictability of ICS response [126]. For example, sputum eosinophil levels have been shown to predict response to ICS [127, 128], and to predict exacerbation risk on ICS withdrawal [129]. In a separate study, titration of ICS treatment according to sputum eosinophil counts resulted in significantly fewer severe exacerbations compared with guideline-driven treatment [130]. However, the analysis of induced sputum is still not widely available for routine use. Further, by using multiple markers of inflammation (FeNO, serum eosinophilic cationic protein concentration, and blood eosinophil count) incremental ICS dosing in persistent asthma is associated with a plateau in symptoms and lung function, but with progressive improvement in inflammatory outcomes and AHR [131]. Unfortunately, the use of either biomarker-based or symptom-based adjustment of ICS is no superior to physician assessment-based adjustment of ICS in terms of time to treatment failure [132].

The variable response to ICS is attributed to different mechanisms underlying airway inflammation [133]. A study using a panel of biomarkers that aimed to identify the presence

of atopic inflammation and oxidative stress for prediction of clinical response to steroids showed that the combination of high FeNO values and high urinary bromotyrosine levels (an indicator of oxidative stress) predicted a favourable clinical response to ICS therapy (in terms of Asthma Control Questionnaire score, FEV_1 and AHR), although the lack of a placebo control limited the validity of the study [126]. A randomised pragmatic trial of ICS optimisation in severe asthma using a composite biomarker algorithm (FeNO, blood eosinophils, serum periostin) to adjust ICS dose versus standard care has been recently proposed [134]. The U-BIOPRED (Unbiased BIOmarkers in PREDiction of respiratory disease outcomes) project is a five-year European-wide project that aims to identify biomarkers for severe asthma [135]. Several biomarkers are currently available and UBIOPRED will help clarify further the potential use of these and other biomarkers in routine practice, and provide evidence for the clinical utility of new potential ones.

A landmark study published more than 20 years ago showed that in patients with persistent symptoms of asthma despite treatment with ICS, the addition of formoterol to budesonide therapy was able to reduce the rate of mild and severe exacerbations, and improved symptoms and lung function without lessening asthma control [76]. Subsequently, a series of other ICS/LABA combinations have demonstrated beneficial effects as maintenance therapy in patients with asthma [6]. For example, the GOAL study demonstrated that a ICS/LABA combination (fluticasone/salmeterol) was more effective than the ICS alone in achieving asthma control over 1 year [136], and the benefit persisted for at least 6 months, with little evidence of loss of control with stable dosing [137]. The concept of achieving better disease control with maintenance ICS/LABA combinations compared to doubling ICS monotherapy in moderate-to-severe asthma has been widened to the use of an ICS/LABA combination as both maintenance and reliever, since such use ensures a timely administration of anti-inflammatory agents in the event of disease worsening [68, 98, 138]. The benefit of giving ICS concomitantly to fast-acting bronchodilators in case of symptom

worsening has been applied also in mild asthma with beclometasone-salbutamol combination [106] and more recently with a budesonide-formoterol combination [66, 67].

Finally, ICS therapy is associated with changes in relative abundance in the lower airway microbiome, particularly with the combination of ICSs and oral corticosteroids impacting on the α- and β-diversity of different bacterial species [139]. Even in patients with mild steroid-naive asthma, differences in the bronchial microbiome are associated with different immunologic and clinical features of the disease, and response to ICS [140].

Conclusions

There is compelling evidence of the value of ICS in improving asthma control, as measured by improved symptoms, pulmonary function and reduced exacerbations. There is, however, less convincing evidence that ICS prevent the decline in pulmonary function that occurs in some, although not all, patients with asthma. Severe exacerbations are associated with a more rapid decline in pulmonary function, and by reducing the risk of severe exacerbations, it is likely that ICS will, at least partially, prevent this decline. Studies using administrative databases also support an important role for ICS in reducing asthma mortality, but the fact that asthma mortality is, fortunately, an uncommon event, make it highly improbable that this will be demonstrated in prospective trials.

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Conflicts of interest

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In the last five years IDP has received speaker's honoraria for speaking at sponsored meetings from Astra Zeneca, Boehringer Ingelheim, Aerocrine, Almirall, Novartis, Teva, Chiesi, Sanofi/Regeneron and GSK and payments for organising educational events from AZ, GSK, Sanofi/Regeneron and Teva. He has received honoraria for attending advisory panels with Genentech, Sanofi/Regeneron, Astra Zeneca, Boehringer Ingelheim, GSK, Novartis, Teva, Merck, Circassia, Chiesi and Knopp and payments to support FDA approval meetings from GSK. He has received sponsorship to attend international scientific meetings from Boehringer Ingelheim, GSK, Astra Zeneca, Teva and Chiesi. He has received a grant from Chiesi to support a Phase 2 clinical trial in Oxford. In 2014-5 he was an expert witness for a patent dispute involving Astra Zeneca and Teva.

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Figure legends

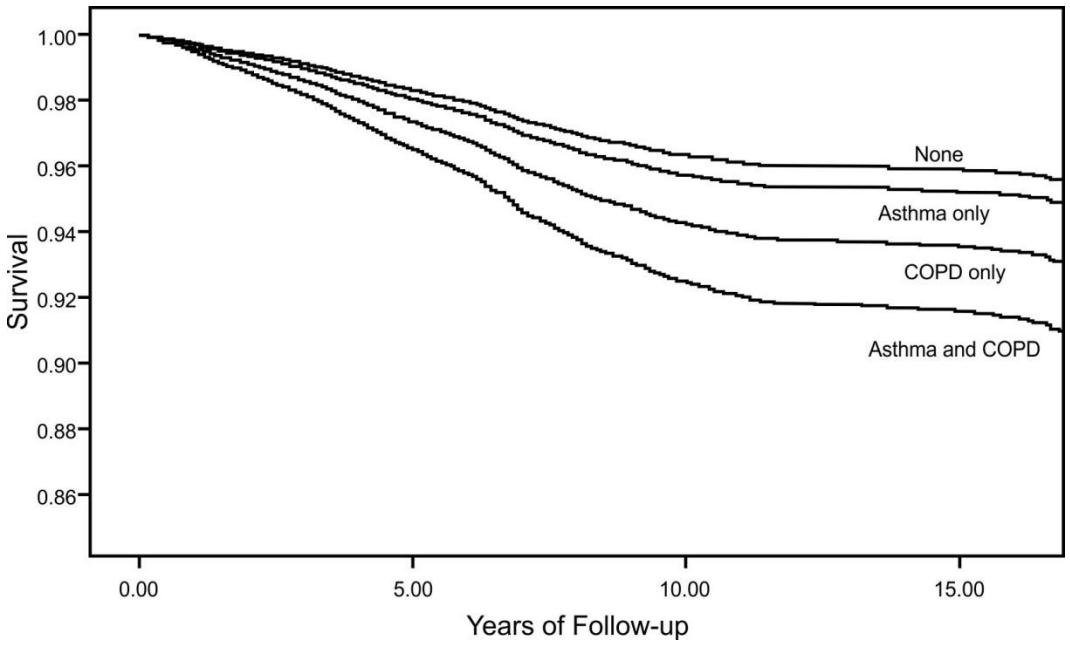
Figure 1. Results from Cox proportion hazard models. Curves are adjusted for sex, age, body mass index, education, race/ethnicity, and smoking status at baseline (reproduced from Diaz-Guzman et al [8] with the permission of the publisher [Taylor & Francis Ltd, http://www.tandfonline.com]).

Footnote: COPD, chronic obstructive pulmonary disease.

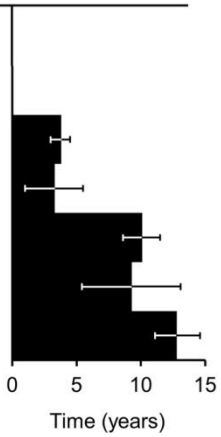
Figure 2. Survival decrease in six subgroups of the Copenhagen City Heart Study, defined by smoking and presence of airway disease (adapted from Lange et al [13], with permission from Elsevier).

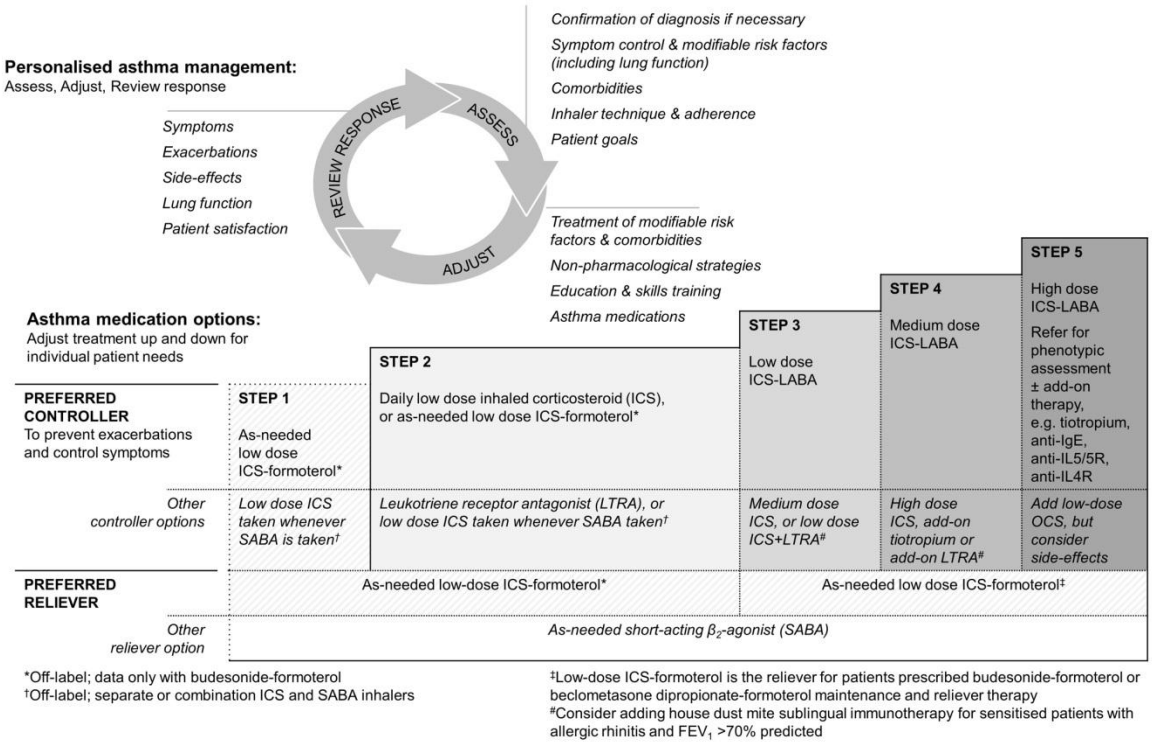
Footnote: COPD, chronic obstructive pulmonary disease; ACO, asthma-COPD overlap. [†]Bias-corrected bootstrap estimates based on Makuch-Ghali curves.

Figure 3. The Global Initiative for Asthma stepwise asthma treatment strategy for adults and adolescents 12+ years of age (reproduced with permission from the Global Initiative for Asthma [65]).


1.00
0.98
0.96
0.94
0.92
0.90
0.88
0.86
Survival
None
Asthma only
COPD only
Asthma and COPD
0.00
5.00
10.00
15.00
Years of Follow-up

	Participants (n)	Survival decrease† (95% CI)	p value
Adjusted for age and sex	**8382**		
Never-smokers without disease	2199	0.0 (reference)	
Ever-smokers without disease	5435	3.8 (3.0 to 4.5)	<0.0001
Asthma	158	3.3 (1.0 to 5.5)	0.004
COPD	320	10.1 (8.6 to 11.5)	<0.0001
ACO with early asthma onset	68	9.3 (5.4 to 13.1)	<0.0001
ACO with late asthma onset	202	12.8 (11.1 to 14.6)	<0.0001





*Off-label; data only with budesonide-formoterol
†Off-label; separate or combination ICS and SABA inhalers
‡Low-dose ICS-formoterol is the reliever for patients prescribed budesonide-formoterol or beclometasone dipropionate-formoterol maintenance and reliever therapy
#Consider adding house dust mite sublingual immunotherapy for sensitised patients with allergic rhinitis and FEV_1 >70% predicted