THERAPEUTIC ADVANCES in
Respiratory Disease

Original Research

Short-acting beta-2 agonist prescription patterns and clinical outcomes in Chinese patients with asthma: an observational study in mainland China for the SABINA programme

Wuping Bao*, Yingying Zhang*, Jingqing Hang, Yubiao Guo, Wei Tang, Chunmei Yun, Jingmin Deng, Meiling Jin, Kefang Lai, Huapeng Yu, Maarten Beekman, Xin Zhou and Min Zhang

Abstract

Objectives: The SABINA CHINA study aimed to determine prescription data for asthma medication with a focus on SABA and ICS in a representative population of patients with asthma in China.

Methods: SABINA China was a multicentre, observational, cross-sectional study with data collected retrospectively from a convenience sample of 25 tertiary centres across China. Patients (age ⩾ 12 years) with ⩾3 consultations/year were enrolled. Data were collected on clinical characteristics, asthma severity, and symptom control (as per GINA 2017), treatment and history of severe exacerbations over the past year. SABA over-prescription was defined as ⩾3 SABA canisters/year. Descriptive statistics are presented.

Results: Between March and August 2020, 498 patients were included in the outcome analysis. Mean (SD) age was 48.7 (15.0) years, 57.9% were female and 91% had moderate-to-severe asthma ($n = 453$). Overall, 12.5% ($n = 62$) and 26.4% ($n = 131$) of patients had uncontrolled and partly controlled asthma, respectively. SABA add-on was prescribed to 20.3% ($n = 101$) of patients; one patient with moderate-to-severe asthma was prescribed SABA-alone. SABA over-prescription in the overall population was 4.0% ($n = 20$; all with moderate-to-severe asthma) and 19.8% (20/101) among those prescribed SABA add-on. In the mild asthma group, 50% ($n = 22$) were prescribed ICS/LABA and 43.2% ($n = 19$) were prescribed LTRA. Among those with moderate-to-severe asthma, 97.4% ($n = 441$) were prescribed ICS/LABA and 55.0% ($n = 249$) were prescribed LTRA. Approximately 30% of patients ($n = 149$) experienced ⩾1% and 6.6% ($n = 33$) ⩾3 severe exacerbations in the preceding year; mean annual number of severe exacerbation/patient was 0.6 (1.2). Among those prescribed SABA add-on, ICS/LABA and LTRA (non-mutually exclusive groups due to overlapping prescriptions), 54.5%, 29.9%, and 35.3% had ⩾1 severe exacerbations, respectively.

Conclusion: Among patients with predominantly moderate-to-severe asthma managed in tertiary care and were prescribed SABA, 1 in 5 received ⩾3 canisters/year. Fewer patients who received ICS/LABA prescriptions experienced annual exacerbations than those prescribed SABA add-on.

Keywords: asthma, China, exacerbation, ICS, over-prescription, overuse, SABA, SABINA

Received: 29 December 2021; revised manuscript accepted: 6 July 2022.

Ther Adv Respir Dis

2022, Vol. 16: 1–14

DOI: 10.1177/17534666221115054

Correspondence to:
Xin Zhou
Department of Pulmonary and Critical Care Medicine, Shanghai General Hospital, Shanghai Jiao Tong University, No. 100, Haining Road, Shanghai 200080, China.
xzhou53@163.com

Min Zhang
Department of Pulmonary and Critical Care Medicine, Shanghai General Hospital, Shanghai Jiao Tong University, No. 100, Haining Road, Shanghai 200080, China.
maggie_zhangmin@163.com

Wuping Bao
Yingying Zhang
Department of Pulmonary and Critical Care Medicine, Shanghai General Hospital, Shanghai Jiao Tong University, Shanghai, China

Jingqing Hang
Department of Pulmonary and Critical Care Medicine, Shanghai Putuo District People's Hospital, Shanghai, China

Yubiao Guo
Department of Pulmonary and Critical Care Medicine, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

Wei Tang
Department of Pulmonary and Critical Care Medicine, Ruijin Hospital, Shanghai Jiao Tong University, Shanghai, China

Chunmei Yun
Department of Pulmonary and Critical Care Medicine, Inner Mongolia Autonomous Region People's Hospital, Hohhot, China

Jingmin Deng
Department of Pulmonary and Critical Care Medicine, The First Affiliated Hospital of Guangxi Medical University, Nanning, China

Meiling Jin
Department of Pulmonary and Critical Care Medicine, Zhongshan Hospital, Fudan University, Shanghai, China

Kefang Lai
State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, National Clinical Research Center for Respiratory Disease, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China

Huapeng Yu
Department of Pulmonary and Critical Care Medicine, Zhujiang Hospital of Southern Medical University, Guangzhou, China

Maarten Beekman
International Medical Respiratory & Immunology, AstraZeneca Netherlands, The Hague, The Netherlands

*Wuping Bao and Yingying Zhang are co-first authors of this study.

Background

In China, the estimated prevalence of asthma in adults (age ⩾ 20 years) is 4.2%, which corresponds to about 45.7 million individuals. Of these, almost 13.1 million experience airflow limitation.[1] Asthma imposes a substantial disease burden in terms of exacerbations leading to hospitalisations, disease progression, impaired quality of life, and mortality. Data from the National China Pulmonary Health Study showed that a substantial proportion of patients with asthma experience exacerbations each year, with 15.5% of patients requiring emergency care and 7.2% requiring hospital admission.[1] Patients with airflow limitation have a higher frequency of exacerbations, with 22.8% requiring emergency room visit and 15.7% requiring hospital admission.[1] Notably, 30–40% of asthma exacerbations requiring emergency care occur in patients with mild asthma.[2–4]

The goals of asthma management are to achieve good control of symptoms, maintain normal activity levels, and minimise the risk of asthma-related exacerbations and death. A paradigm shift in asthma management occurred in 2019 when the Global Initiative for Asthma (GINA) report recommended that adults and adolescents with asthma should not be treated with short-acting beta-2 agonists (SABA) alone, given the poor exacerbation and mortality outcomes associated with this therapy.[5,6] As asthma is characterised by chronic airway inflammation, recent GINA reports (2019 onwards) recommend inhaled corticosteroid (ICS)-containing treatment for all adolescents and adults with asthma, regardless of disease severity. Specifically, for patients with moderate-to-severe disease, a regular ICS-containing (preferably ICS-formoterol) maintenance therapy is recommended for symptom control and to reduce the risk of acute exacerbations. These recommendations were extended to patients with mild disease, and ICS-formoterol is recommended as the preferred sole reliever therapy to be used as needed. The recommendations are based on evidence from several trials, which have demonstrated a significant reduction in exacerbations with budesonide–formoterol as-needed treatment in patients with mild[7,8] or moderate-to-severe asthma.[9,10]

In China, asthma is generally underdiagnosed and undertreated due to the lack of appropriate primary-care services, especially in rural regions. The China Pulmonary Health Study, conducted in a nationally representative sample of the general Chinese adult population aged ⩾20 years (N = 50,991), revealed an asthma prevalence rate of 4.2%; of these, only 28.8% of patients with asthma had received a prior diagnosis and 23.4% had ever undergone pulmonary function tests. Among respondents with asthma, only 5.6% used inhaled corticosteroids for treatment.[1] Furthermore, in clinical practice, a significant proportion of patients with asthma receive over-prescription of SABA and/or under-prescription of ICS, compared to treatment recommendations,[11] and the inappropriate prescription of these medications leads to an increased burden of disease. For example, a survey of Chinese patients with mild asthma revealed that only 22% of patients received low-dose ICS therapy.[12] About 18% of these patients experienced exacerbations for 12 months (11% and 20% in patients receiving Step 1 and Step 2 treatment, respectively, as per GINA 2016 report). In addition, a high proportion of patients with asthma have uncontrolled symptoms (55%, as assessed by the Asthma Control Test),[13] including those with mild disease (12% uncontrolled and 74% partly controlled, as assessed by GINA criteria).[12] Therefore, data on prescription patterns and prevalence of inappropriate SABA use are needed to understand the public health burden of SABA over-reliance and assist policymakers and clinicians in assessing the potential benefits of switching to ICS-containing relievers as the standard of care in asthma management.

SABA use IN Asthma (SABINA) III is part of the SABINA observational studies that were designed to capture the current burden of SABA use and its impact on asthma-related clinical outcomes on a global scale.[14] Results from SABINA III, which comprised patients from 24 countries, showed that approximately 38% of patients with asthma received over-prescription of SABA, which was associated with a 40–92% higher risk of severe exacerbations, depending on the number of over-prescriptions received.[15] In this real-world, non-interventional, cross-sectional, multicentre study, which was conducted as part of the global SABINA III programme, we assess the treatment patterns and clinical outcomes in patients with predominantly moderate-to-severe asthma, who were managed at tertiary-care centres across mainland China.

Methods

Study population

Eligible patients were aged ⩾12 years, with a documented diagnosis of asthma according to the investigator (confirmed by the presence of recurrent symptoms and lung function test), as well as ⩾3 annual consultations with the physician at the time of enrolment. The exclusion criteria included a diagnosis of chronic obstructive pulmonary disease or other chronic respiratory diseases other than asthma, or any acute or chronic medical condition that, in the investigator's opinion, would limit the patient's ability to participate in this study. No additional restrictions for inclusion or exclusion were employed to ensure that the enrolled patients are representative of the real-world patient population in Tier 3 hospitals in China. All enrolled patients (or legal guardians) provided written informed consent for participation in the study.

Study design

This was a multicentre, observational, cross-sectional study with retrospective data collection conducted with a convenience sample of 25 tertiary centres (specialists) located across China. Consecutive patients attending health clinics for at least three annual consultations were enrolled in the study between March and August 2020. Data were collected either retrospectively from existing patient medical records (both electronic and paper) or in real time by investigators during a clinic visit, using a centrally designed electronic case report form. In addition, patients were asked about SABA purchase over the counter from the pharmacy in the past 12 months. No additional interventions to routinely performed physician visits, examinations or treatments were required, other than the 2017 GINA assessment of asthma control. Any procedure ordered by the physician during the study was in line with the routine clinical care delivered to the patient at the discretion of the participating physician. There were no follow-up visits, and all data were collected using existing medical records and/or during one designated study visit.

The study was conducted in accordance with the guidelines set forth by the International Society for Pharmacoepidemiology and the International Society for Pharmacoeconomics and Outcomes Research for the conduct of burden of disease studies.

Data variables

Data were collected on demographics, lifestyle, disease characteristics [diagnosis and severity according to 2017 GINA guidelines; mild [Step(Step 1: SABA only; Step 2: low-dose ICS ±];); moderate [Step(Step 3: low-dose ICS + LABA ±];); Severe [Step(Step 4: medium dose ICS + add-on maintenance medication ±);]; Step 5: high dose ICS + add-on maintenance medication ± SABA]), medical history and comorbidities, asthma-prescribed treatments (therapeutic class, device, modality, posology) and history of severe exacerbations in the previous 12 months, as well as the 2017 GINA assessment of asthma control.

SABA use was estimated using the average number of prescriptions of inhalers/canisters of SABA per year. The GINA report recommends stepping up treatment from Step 1 to 2 at the threshold of 3 SABA puffs/week. Therefore, 'appropriate' SABA prescriptions were defined according to this threshold, as an average use of less than 3 puffs/week, which equates to a cut-off of less than 150 puffs/actuations per year. Although the SABA dose per actuation depends on the inhaler type and drug, the GINA report specifies the threshold of three puffs regardless of dosage per actuation. The majority of inhalers contain 100 or 200 actuations. To enable comparison of different types and number of doses in the SABA canisters, a standardised threshold for appropriate use of SABA was defined as 150 doses/puffs/actuations per year, approximating ⩽2 canisters per year.[16–18] SABA over-prescription in this study was defined as the collection of ⩾3 SABA canisters annually.[16] During the baseline period, patients were grouped by the number of collected SABA canisters: ⩽2, 3–5, 6–9, and 10–12.

Based on the number of SABA and ICS prescriptions over the preceding 12 months, patients with mild asthma were grouped into five categories: (1) no prescriptions for asthma inhalers, (2) appropriate SABA prescription with no ICS, (3) appropriate SABA prescription with ICS, (4) SABA over-prescription with no ICS, and (5) SABA over-prescription with ICS. Similarly, patients with moderate-to-severe asthma were grouped into two categories: (1) appropriate SABA prescription on top of maintenance therapy and (2) SABA over-prescription on top of maintenance therapy.

Table 1. Severity of asthma.

Stage, *n* (%)	Total (*N* = 498)
Mild asthma (GINA treatment steps 1–2)	45 (9)
Step 1	21 (4.2)
Step 2	24 (4.8)
Moderate-to-severe asthma (GINA treatment steps 3–5)	453 (91)
Step 3	212 (42.6)
Step 4	201 (40.4)
Step 5	40 (8)

GINA, Global Initiative for Asthma.

Study outcomes

The primary outcome of the study was to determine the pattern and trend of SABA (canisters per year) and ICS prescriptions (by average daily dose) in a population of patients with asthma in China. Data on over-the-counter (OTC) SABA purchases from a pharmacy in the past 12 months was also obtained. Secondary outcomes included distribution of demographic and clinical features for the asthma population, prevalent symptoms (2017 GINA assessment of asthma control) and the proportion of patients experiencing severe exacerbations (defined as those leading to use of systemic corticosteroids, hospitalisation or emergency room visit) related to asthma in the past 12 months for patients who received prescription for SABA or other drug categories.

Statistical analyses

All variables were analysed descriptively with appropriate statistical methods, which included categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (e.g. mean and standard deviation [SD]).

Results

Patient demographics and clinical characteristics

A total of 499 patients were enrolled between March and August 2020, and 498 were included in the analysis set; one patient was excluded from the analyses due to an asthma duration lasting less than 12 months. All patients were managed by specialists (pulmonologists), and the vast majority of patients had moderate-to-severe asthma ($n = 453$, 91%). Only 45 (9%) patients with mild asthma were included in the study (Table 1).

Mean (SD) age of the study population was 48.7 (15.0) years and more than half were female (57.9%). Mean (SD) body mass index (BMI) was 23.7 (3.4) kg/m^2 and 32.6% were overweight or obese (BMI $\geqslant$ 25 kg/m^2). Almost half of the study population had one or two comorbidities (48.5%) and 34.8% had no comorbidities (Table 2). More than three-quarters of the study population (76.3%) had partially reimbursable healthcare insurance and only 10.3% had a fully reimbursable healthcare plan. A comparison of baseline demographics and clinical characteristics between mild and moderate-to-severe asthma groups is presented in Table 2. Patients with moderate-to-severe asthma were older (49.2 *vs* 43.7 years), more likely female (60.0% *vs* 36.4%), and more likely to have comorbidities (66% *vs* 59%).

Treatment patterns

The prescription patterns for the asthma treatment are summarised in Figure 1. The various categories of SABA prescriptions in Chinese patients with asthma managed at speciality care are summarised in Table 3. SABA-alone was prescribed to only one patient (0.2%) with moderate-to-severe asthma, while as an add-on to maintenance therapy SABA was prescribed in 20.3% ($n = 101$) of patients. The median (range) duration of SABA add-on use was 61 (30,244) days. Overall, 79.8% of patients ($n = 396$) received no SABA prescriptions in the preceding 12 months; corresponding percentages among mild and moderate-to-severe asthma groups were 90.9% ($n = 40$) and 78.8% ($n = 356$), respectively. About 16.1% ($n = 80$) were prescribed $\leqslant$2 SABA canisters, with 9.1% ($n = 4$) of patients with mild asthma and 16.8 ($n = 76$) of those with moderate-to-severe asthma prescribed $\leqslant$2 SABA canisters. Overall, the prevalence of SABA over-prescription ($\geqslant$3 canisters) was 4.0% (20/496), and all these patients had moderate-to-severe asthma. However, among those who were prescribed SABA add-on therapy, the prevalence of SABA over-prescription was 19.8% (20/101). Additional OTC purchase of SABA without prescription was observed in 5.2% ($n = 26$) of patients; among these, 50% ($n = 13$) purchased $\geqslant$3 canisters (Supplementary Table 1).

Table 2. Patient demographics and clinical characteristics.

Variable	Patients enrolled by specialists based on severity of asthma		Total (*N* = 498)[a]
	Mild asthma (*N* = 45)[a]	Moderate-to-severe asthma (*N* = 453)	
Age, mean (SD)	43.7 (17.3)	49.2 (14.7)	48.7 (15.0)
Female, *n* (%)	16 (36.4)	272 (60.0)	288 (57.9)
BMI (kg/m^2), mean (SD)	23.3 (3.5)	23.7 (3.4)	23.7 (3.4)
BMI ⩾ 18.5–24.9, *n* (%)	26 (59.1)	283 (62.5)	309 (62.2)
BMI ⩾ 25–29.9, *n* (%)	14 (31.8)	131 (28.9)	145 (29.2)
BMI ⩾ 30, *n* (%)	1 (2.3)	16 (3.5)	17 (3.4)
Smoking status, *n* (%)			
Active smoker	4 (9.1)	26 (5.7)	30 (6.0)
Former smoker	7 (15.9)	68 (15.0)	75 (15.1)
Never smoker	33 (75.0)	359 (79.2)	392 (78.9)
Education level, *n* (%)			
Primary school	2 (4.5)	36 (7.9)	38 (7.6)
Secondary school	7 (15.9)	102 (22.5)	109 (21.9)
High school	11 (25)	107 (23.6)	118 (23.7)
University and higher	24 (54.5)	203 (44.8)	227 (45.7)
Unknown	0 (0.0)	5 (1.1)	5 (1.0)
Healthcare insurance or medical funding, *n* (%)			
Not reimbursed	5 (11.4)	57 (12.6)	62 (12.5)
Partially reimbursed	34 (77.3)	345 (76.2)	379 (76.3)
Fully reimbursed	5 (11.4)	46 (10.2)	51 (10.3)
Unknown	0 (0.0)	5 (1.1)	5 (1.0)
Comorbidities, *n* (%)			
No comorbidities	18 (40.9)	155 (34.2)	173 (34.8)
1–2 comorbidities	18 (40.9)	223 (49.2)	241 (48.5)
3–4 comorbidities	4 (9.1)	49 (10.8)	53 (10.7)
5 or more comorbidities	4 (9.1)	26 (5.7)	30 (6.0)

BMI, body mass index; SD, standard deviation.
[a]One patient (mild asthma group) was followed-up at the rehabilitation physiotherapy department and was not included in the analysis set of patients enrolled by specialists (pulmonologist).

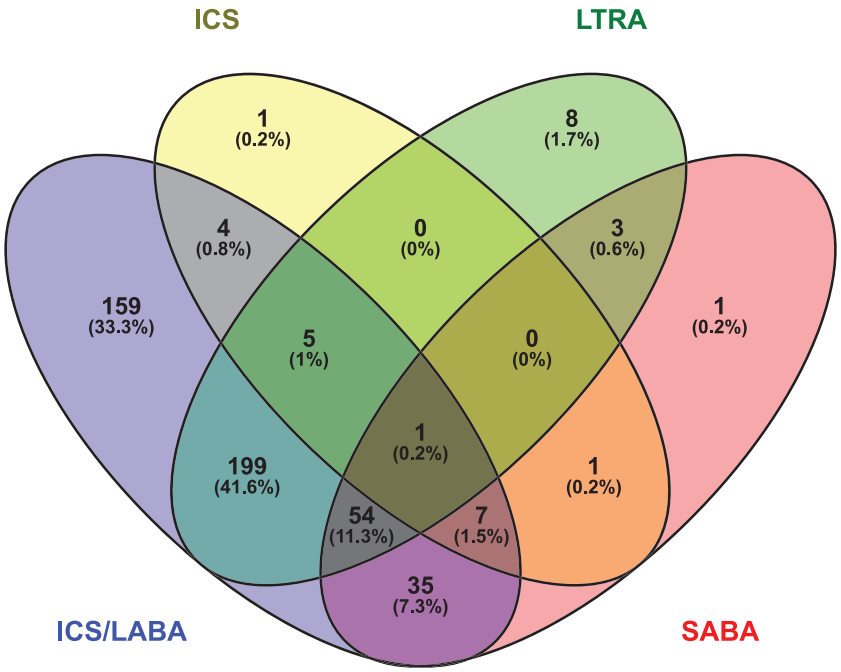

Figure 1. Venn diagram illustration of prescription patterns in patients with asthma. Data are presented for 478 of the 498 patients enrolled. Of the 20 patients for which data are not presented in the figure, four patients received prescriptions for other treatments (one patient each reporting prescription for methoxyphenamine, doxofylline, acetylcysteine, and doxofylline in combination with zhichaunlingkoufuye and cefmetazole sodium). The remaining 16 patients (including 12 with mild asthma and 4 with moderate-to-severe asthma) did not report any treatment prescriptions. Data are presented as number of patients (percentage of study population). Of 478 patients included in the analysis, 259 were prescribed ICS/LABA and LTRA, 97 were prescribed ICS/LABA and SABA (alone or as add-on), 58 were prescribed LTRA and SABA (alone or as add-on), 9 were prescribed ICS and SABA (alone or as add-on), 6 were prescribed ICS and LTRA, and only 1 patient was prescribed ICS/LABA, SABA, ICS, and LTRA.
ICS, inhaled corticosteroids; LABA, long-acting beta-agonists; LTRA, leukotriene receptor antagonists; SABA, Short-Acting Beta-2 Agonist.

In an analysis of SABA and ICS prescriptions in patients with mild asthma, ⩽2 canisters of SABA with ICS were prescribed for 6.8% of patients. None of the patients with mild asthma received SABA over-prescription (⩾3 canisters) with or without ICS. Among patients with moderate-to-severe asthma, the prevalence of SABA over-prescription as add-on to maintenance therapy was 4.4% (20/452). Of note, more than half of the study population was prescribed leukotriene receptor antagonist (LTRA), mostly in combination with maintenance treatment (53.9%, $n=268$), with a median duration of 30 days. About 43% ($n=19$) of patients with mild asthma and 55% ($n=249$) with moderate-to-severe asthma received LTRA therapy.

ICS alone was prescribed in 3.6% ($n=18$) of patients, mostly in those with moderate-to-severe asthma (15/18). Overall, most patients were prescribed a fixed-dose combination of ICS/long-acting beta-agonists (LABA; 93.2%, $n=463$; median duration of use: 91 days), with the vast majority of patients with moderate-to-severe asthma receiving a prescription for ICS/LABA (97.4%, 441/453; mean duration of use: 101.3 days). Fifty percent (22/44) of the patients with mild asthma were prescribed ICS/LABA combination therapy. A total of 82 (16.5%) patients were prescribed oral corticosteroid (OCS) burst treatment (either for the management of severe exacerbations or due to increased symptoms), and 37 (7.4%) were prescribed OCS long-term maintenance treatment; this was mostly in patients with moderate-to-severe asthma (Table 4). Antibiotics for asthma were prescribed in 9.6% of patients, with a slightly higher proportion of patients with mild asthma receiving antibiotic prescriptions compared to those with moderate-to-severe asthma (14% *vs* 9.1%).

Table 3. SABA and ICS prescriptions in patients with asthma.

Treatment	Patients enrolled by specialists based on severity of asthma		Total ($N=498$)[a,b]
	Mild asthma ($N=45$)[a]	Moderate-to-severe asthma ($N=453$)[b]	
SABA prescriptions, *n* (%)			
0	40 (90.9)	356 (78.8)	396 (79.8)
1–2	4 (9.1)	76 (16.8)	80 (16.1)
3–5	0 (0.0)	12 (2.7)	12 (2.4)
6–9	0 (0.0)	3 (0.7)	3 (0.6)
10–12	0 (0.0)	5 (1.1)	5 (1.0)
SABA and ICS prescriptions, *n* (%)			
No prescriptions for asthma inhalers	41 (93.2)	NA	
⩽2 SABA canisters prescription with ICS	3 (6.8)	NA	
SABA and ICS prescriptions, *n* (%)			
⩽2 SABA canisters prescription on top of maintenance therapy	NA	432 (95.6)	
⩾3 SABA canisters prescription on top of maintenance therapy	NA	20 (4.4)	

ICS, inhaled corticosteroids; NA, not available; SABA, Short-Acting Beta-2 Agonist.
[a]One patient (mild asthma group) was followed-up at the rehabilitation physiotherapy department and was not included in the analysis set of patients enrolled by specialists (pulmonologist).
[b]Number of missing values: $n=1$.

Asthma disease characteristics and exacerbations

Mean (SD) duration of asthma was 11.2 (14.5) years; this was higher in the moderate-to-severe than the mild asthma group (11.5 *vs* 8.7 years; Table 5). Overall, 29.9% ($n=149$) of the study population experienced at least one severe exacerbation in the previous 12 months; 6.6% ($n=33$) of patients had three or more severe exacerbations in that time. Among patients with mild asthma, 90.9% ($n=40$) experienced no exacerbations and 9.1% ($n=4$) of patients experienced one severe exacerbation in the preceding year (none of the patients had more than one exacerbation). Among patients with moderate-to-severe asthma ($N=453$), 68.0% ($n=308$) experienced no exacerbations, 32.0% ($n=145$) had at least one exacerbation and 7.3% ($n=33$) had three or more severe exacerbations in the previous 12 months (Table 5). Mean (SD) number of severe asthma exacerbations in that time was 0.6 (1.2); the number of severe exacerbations was higher in patients with moderate-to-severe than mild asthma (0.6 [1.3] *vs* 0.1 [0.3]).

The proportion of patients with moderate-to-severe asthma experiencing severe exacerbations by treatment groups (non-mutually exclusive groups) is presented in Table 6. Among patients who were prescribed SABA add-on therapy, 54.5% (55/101) had at least one exacerbation in the preceding 12 months. Half of the patients who received over-prescription of SABA experienced severe exacerbation (50%; 9/18). Conversely, 31.6% (6/19) and 29.9% (139/464) of patients who were prescribed ICS and ICS/LABA therapy, respectively, experienced severe exacerbations. Among those prescribed LTRA therapy, 35.3% (95/269) had at least one exacerbation. Frequency of exacerbations was higher for patients who were prescribed OCS, a short- (85.4%, 70/82) or long-term (67.6%, 25/37) course, and antibiotics (68.1%, 32/47).

Table 4. Treatment for asthma.

Treatment	Patients enrolled by specialists based on severity of asthma		Total (*N* = 498)[a]
	Mild asthma (*N* = 45)[a]	Moderate-to-severe asthma (*N* = 453)	
SABA-alone, *n* (%)	0 (0.0)	1 (0.2)	1 (0.2)
Total use in the last 12 months (canisters/inhalers), median (min, max)	NA	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)
SABA add-on to maintenance therapy, *n* (%)	4 (9.1)	97 (21.4)	101 (20.3)
0–2	4 (100)	76 (79.2)	80 (80)
3–5	–	12 (12.5)	12 (12)
6–9	–	3 (3.1)	3 (3)
10–12	–	5 (5.2)	5 (5)
Missing values, *n* (%)	0 (0)	1 (1.0)	1 (0.9)
Total use in the last 12 months (canisters/inhalers), median (min, max)	1.0 (1.0, 1.0)	1.0 (1.0, 12.0)	1.0 (1.0, 12.0)
Duration of use (days), median (min, max)	61.0 (61.0, 61.0)	61.0 (30.0, 244.0)	61.0 (30.0, 244.0)
ICS, *n* (%)	3 (6.8)	15 (3.3)	18 (3.6)
Total use in the last 12 months (canisters/inhalers), median (min, max)	2.0 (1.0, 3.0)	2.0 (1.0, 20.0)	2.0 (1.0, 20.0)
Total daily dose, *n* (%)			
Low dose	3 (100)	13 (86.7)	16 (88.9)
Medium dose	0 (0)	2 (13.3)	2 (11.1)
High dose	0 (0)	1 (6.7)	1 (5.6)
Duration of use (days), median (min, max)	213.5 (183.0, 244.0)	91.5 (31.0, 122.0)	122.0 (31.0, 244.0)
ICS/LABA (fixed-dose combination), *n* (%)	22 (50)	441 (97.4)	463 (93.2)
Total daily dose, *n* (%)			
Low dose	20 (90.9)	209 (47.4)	229 (49.5)
Medium dose	2 (9.1)	207 (46.9)	209 (45.1)
High dose	0 (0)	25 (5.7)	25 (5.4)
Duration of use (days), median (min, max)	91.0 (30.0, 365.0)	91.0 (30.0, 275.0)	91.0 (30.0, 365.0)
LTRA, *n* (%)	19 (43.2)	249 (55.0)	268 (53.9)
Duration of use (days), median (min, max)	30.0 (0.0, 365.0)	30.0 (0.0, 365.0)	30.0 (0.0, 365.0)
OCS treatment short course, *n* (%)	1 (2.3)	81 (17.9)	82 (16.5)
Total daily dose (mg/day), median (min, max)	5.0 (5.0, 5.0)	20.0 (5.0, 180.0)	20.0 (5.0, 180.0)

(Continued)

Table 4. (Continued)

Treatment	Patients enrolled by specialists based on severity of asthma		Total (*N* = 498)[a]
	Mild asthma (*N* = 45)[a]	Moderate-to-severe asthma (*N* = 453)	
Number of days per prescription, median (min, max)	10.0 (10.0, 10.0)	4.5 (1.0, 30.0)	5.0 (1.0, 30.0)
OCS long-term/maintenance dosing, *n* (%)	0 (0)	37 (8.2)	37 (7.4)
Total exposure over 12 months (g), median (min, max)	–	0.6 (0.0, 500.0)	0.6 (0.0, 500.0)
Total daily dose (mg/day), median (min, max)	–	12.0 (2.0, 45.0)	12.0 (2.0, 45.0)
Antibiotics (prescribed for asthma only), *n* (%)	6 (14.0)	41 (9.1)	47 (9.6)

ICS, inhaled corticosteroids; LABA, long-acting beta-agonists; LTRA, leukotriene receptor antagonists; NA, not available; OCS, oral corticosteroids; SABA, Short-Acting Beta-2 Agonist.
[a]One patient (mild asthma group) was followed-up at the rehabilitation physiotherapy department and was not included in the analysis set of patients enrolled by specialists (pulmonologist).

Table 5. Asthma disease characteristics, severe exacerbations, and asthma control.

Disease characteristics	Patients enrolled by specialists based on severity of asthma		Total (*N* = 498)[a]
	Mild asthma (*N* = 45)[a]	Moderate-to-severe asthma (*N* = 453)	
Asthma duration (years), mean (SD)	8.7 (12.3)	11.5 (14.7)	11.2 (14.5)
Number of severe exacerbations in the last 12 months, mean (SD)	0.1 (0.3)	0.6 (1.3)	0.6 (1.2)
Patients with severe exacerbations in the last 12 months, *n* (%)			
0 exacerbation	40 (90.9)	308 (68.0)	348 (70.0)
1 exacerbation	4 (9.1)	76 (16.8)	80 (16.1)
2 exacerbations	0 (0)	36 (7.9)	36 (7.2)
3 exacerbations	0 (0)	18 (4.0)	18 (3.6)
More than 3 exacerbations	0 (0)	15 (3.3)	15 (3.0)
Asthma symptom control as assessed by GINA treatment step (2017), *n* (%)			
Well-controlled	34 (77.3)	270 (59.6)	304 (61.2)
Partly controlled	9 (20.5)	122 (26.9)	131 (26.4)
Uncontrolled	1 (2.3)	61 (13.5)	62 (12.5)

GINA, Global Initiative for Asthma; SD, standard deviation.
[a]One patient (mild asthma group) was followed-up at the rehabilitation physiotherapy department and was not included in the analysis set of patients enrolled by specialists (pulmonologist).

Table 6. Asthma control levels and severe exacerbations in patients with moderate-to-severe asthma by treatment.

Disease characteristics	Treatment							Total (*N* = 453)
	SABA as add-on (*n* = 97)	ICS (*n* = 15)	ICS/LABA (FDC) (*n* = 441)	OCS short course (*n* = 81)	OCS long term (*n* = 37)	Antibiotics (*n* = 41)	LTRA (*n* = 249)	
No. patients with severe exacerbations in the last 12 months								
0 exacerbation	43 (44.3)	9 (60.0)	305 (69.2)	12 (14.8)	12 (32.4)	12 (29.3)	156 (62.7)	308 (68.0)
1 exacerbation	27 (27.8)	3 (20.0)	72 (16.3)	33 (40.7)	10 (27.0)	13 (31.7)	55 (22.1)	76 (16.8)
2 exacerbations	13 (13.4)	NA	35 (7.9)	19 (23.5)	6 (16.2)	9 (22.0)	20 (8.0)	36 (7.9)
3 exacerbations	6 (6.2)	2 (13.3)	15 (3.4)	8 (9.9)	5 (13.5)	4 (9.8)	8 (3.2)	18 (4.0)
4 exacerbations	2 (2.1)	1 (6.7)	5 (1.1)	2 (2.5)	1 (2.7)	NA	4 (1.6)	5 (1.1)
5 exacerbations	2 (2.1)	NA	4 (0.9)	3 (3.7)	1 (2.7)	2 (4.9)	2 (0.8)	5 (1.1)
More than 5 exacerbations	4 (4.1)	NA	5 (1.1)	4 (4.9)	2 (5.4)	1 (2.4)	4 (1.6)	5 (1.1)
Asthma symptom control level								
Partly controlled	23 (23.7)	6 (40.0)	117 (26.5)	19 (23.5)	12 (32.4)	13 (31.7)	68 (27.3)	122 (26.9)
Uncontrolled	26 (26.8)	2 (13.3)	58 (13.2)	23 (28.4)	9 (24.3)	12 (29.3)	39 (15.7)	61 (13.5)
Well-controlled	48 (49.5)	7 (46.7)	266 (60.3)	39 (48.1)	16 (43.2)	16 (39.0)	142 (57.0)	270 (59.6)

FDC, fixed-dose combination; ICS, inhaled corticosteroids; LABA, long-acting beta-agonists; LTRA, leukotriene receptor antagonists; NA, not available; OCS, oral corticosteroids; SABA, Short-Acting Beta-2 Agonist.

Symptom control

Overall, 12.5% ($n = 62$) of patients had uncontrolled asthma symptoms, and 26.4% ($n = 131$) had partly controlled symptoms (Table 4). A higher proportion of patients with moderate-to-severe asthma had uncontrolled disease compared with those with mild asthma (13.5% *vs* 2.3%). The proportion of patients with mild and moderate-to-severe asthma with well-controlled symptoms was 77.3% and 59.6%, respectively. Among patients who were prescribed SABA add-on therapy, 51.5% (52/101) had partially controlled or uncontrolled symptoms. Conversely, 38.8% (180/464) and 40.9% (110/269) of patients who were prescribed ICS/LABA and LTRA therapy had partly controlled or uncontrolled symptoms, respectively.

Discussion

The proportion of patients who were prescribed SABA therapy was low in the Chinese tertiary-care setting (20%). Among those who were prescribed this therapy, 1 in 5 patients received SABA over-prescription (⩾3 canisters/year). A small subset of patients in our study also purchased OTC SABA directly from a pharmacy without a prescription; among these patients, 50% purchased ⩾3 canisters/year, indicating the need for patient education on SABA issues. Overall, the vast majority (93.2%) of Chinese patients with asthma who were managed at tertiary care centres were prescribed ICS/LABA fixed-dose combination therapy, with a higher frequency observed in patients with moderate-to-severe disease (>97%). The proportion of patients with mild asthma-prescribed ICS/LABA was low, with only 50% prescribed this therapy. Of note, more than 50% of patients with asthma were also prescribed LTRA mostly in combination with maintenance treatment. Another key observation was the high frequency of antibiotic prescriptions in patients with mild asthma. This may be because of the overlapping and non-specific symptoms of mild asthma and respiratory tract infections, as well as due to poor treatment

compliance among patients with mild asthma. Long-term or maintenance OCS therapy was prescribed in 8% of patients with moderate-to-severe asthma, with a mean duration of 81 days.

Approximately 70% of patients did not experience an exacerbation in the previous 12 months; however, among those with moderate-to-severe disease, almost 1 in 3 patients experienced at least one severe exacerbation (32%), and 7.3% had three or more severe exacerbations in that time. In addition, 40% of patients with moderate-to-severe asthma and 23% of those with mild disease had partly controlled or uncontrolled symptoms. These findings are comparable with that reported in the nationwide China Pulmonary Health Study, where 15.5% of patients needed to present to the emergency department and 7.2% were hospitalised due to an exacerbation in the preceding 12 months.[1] However, in patients with airflow limitation, 22.8% experienced exacerbations requiring emergency care and 15.7% required hospital admission. In the Asia-Pacific Asthma Insights and Management study, 67% of Chinese patients with asthma reported experiencing exacerbation in asthma symptoms (of any severity) in the preceding 12 months.[19]

The low prescription frequency of SABA therapy in this study is in contrast with that observed in other countries included in the SABINA programme.[20–22] In the pan-international SABINA III study, 38% of patients with asthma were prescribed ⩾3 SABA canisters and 18% purchased OTC SABA.[15] In the SABINA Asia study, 26% of patients with asthma were over-prescribed SABA. In the SABINA Malaysia study, nearly half (47.4%) of all asthma patients were over-prescribed SABA, and this percentage did not change based on treatment facility (primary or speciality care).[15] The prevalence of SABA over-prescription in European countries ranged from 9% to 38%.[20–22] Hence, it is important to view the results of this study in the context of the study population. First, our study did not include patients that were treated at primary care, where a large majority of patients, particularly those with mild disease, are managed. For example, in a study of asthma management patterns in Taiwan, it was found that almost 76% of asthma patients were managed by internists or family physicians, and 12% were managed by specialists. Hence, the study results do not reflect the SABA prescription patterns in primary care. Instead, these results may reflect a better case scenario since patients were managed by specialists in tertiary care, which has a higher level of compliance with GINA recommendations than primary care. Furthermore, more than half of the patients with asthma were prescribed LTRA for a long duration; this is in line with LTRA use in other countries – for example, a retrospective cohort study of medical and pharmacy claims database in the United States showed that 62% of patients who initiated triple therapy, received LTRA.[23] Evidence from several studies that investigated the efficacy of ICS/LABA compared with ICS + LTRA showed superior benefits on lung function and exacerbations in favour of ICS/LABA;[24,25] however, we could not compare the effects of ICS + LTRA and ICS/LABA in this study due to overlapping prescriptions. Despite enrolling patients managed at tertiary-care centres, our study included multiple centres with wide geographical representation across China, and the frequency of SABA over-prescription was substantially lower than that observed among patients managed at tertiary-care centres in other countries.[15,20,26,27]

Despite the low prescription frequency of SABA therapy, more than half (54.5%) of the patients who were prescribed SABA experienced a severe exacerbation, indicating an increased risk of exacerbations in patients receiving this therapy. In addition, the long duration of SABA therapy (average duration of use: 97 days) indicates poor asthma control in these patients, which may have prompted increased prescriptions for SABA therapy. Furthermore, patients who purchase OTC SABA directly from a pharmacy, without a prescription, are more likely to use ⩾3 canisters of SABA. Although we have not assessed whether SABA over-prescription is associated with an increased incidence of exacerbation, results from the pan-international SABINA III study showed that SABA over-prescription (⩾3 SABA canisters) was associated with a 40–92% higher risk of severe exacerbation and 36–67% lower likelihood of controlled or partly controlled asthma, compared with those prescribed ⩽2 SABA canisters.[15] In addition, previous studies have demonstrated a significant association between SABA over-prescription and increased risk of exacerbations and respiratory and asthma-related deaths.[21,22,28,29] Accordingly, the recent GINA report recommends against the use of SABA-alone therapy in patients with asthma and recommends ICS-formoterol therapy (as needed) in patients with mild asthma.[6]

A key strength of this study is the nationwide perspective, thus providing insights into the real-world asthma management practices in tertiary-care settings in China. Data on the history of exacerbations (including treatment for exacerbations) in the preceding 12 months was collected to avoid seasonal factors. The study results represent robust and reliable data on clinical practice as collected by specialists. However, the study did not enrol patients from non-specialist and primary-care centres in mainland China; hence, it may not reflect management practices in these healthcare centres. In addition, the lack of data from primary-care centres and a low number of patients with mild disease could have limited insights into the management patterns of a large proportion of asthma patients. Furthermore, the study population received prescriptions for a variety of treatments, making it difficult to analyse the exacerbation data by different treatment patterns (such as SABA + ICS, SABA + ICS/LABA, ICS/LABA + LTRA); thus, appropriately designed studies are needed to determine which treatment pattern is most likely to provide maximum benefit in clinical practice.

Conclusion

In conclusion, the findings from this nationwide SABINA study demonstrated a low prescription frequency of SABA therapy among predominantly moderate-to-severe asthma patients managed at tertiary care centres in China. However, among those who received SABA prescriptions, 1 in 5 patients received ⩾3 canisters per year and more than half experienced a severe exacerbation in the preceding year. Prescriptions for the evidence-based ICS/LABA fixed-dose combination therapy were high, and fewer patients receiving ICS/LABA treatment experienced annual exacerbations than those receiving SABA prescriptions. Further reduction in SABA prescriptions through the use of a reliever with anti-inflammatory properties, such as an ICS-formoterol fixed-dose combination therapy and as recommended by the latest guidelines, may further improve clinical outcomes.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Bao Wuping: Conceptualisation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing – original draft; Writing – review & editing.

Zhang Yingying: Conceptualisation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing – original draft; Writing – review & editing.

Hang Jingqing: Conceptualisation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing – original draft; Writing – review & editing.

Guo Yubiao: Conceptualisation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing – original draft; Writing – review & editing.

Tang Wei: Conceptualisation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing – original draft; Writing – review & editing.

Yun Chunmei: Conceptualisation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing – original draft; Writing – review & editing.

Deng Jingmin: Conceptualisation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing – original draft; Writing – review & editing.

Jin Meiling: Conceptualisation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing – original draft; Writing – review & editing.

Lai Kefang: Conceptualisation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing – original draft; Writing – review & editing.

Yu Huapeng: Conceptualisation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing – original draft; Writing – review & editing.

Beekman Maarten: Conceptualisation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing – original draft; Writing – review & editing.

Zhou Xin: Conceptualisation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing – original draft; Writing – review & editing.

Zhang Min: Conceptualisation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing – original draft; Writing – review & editing.

Acknowledgements

The authors would like to thank Dr Lin Dang (Suzhou Municipal Hospital), Dr Lei Wei (The First Affiliated Hospital of Suzhou University), Dr Guo Xuejun (Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine), Dr Qiu Chen (Shenzhen People's Hospital), Dr Cao Jie (Tianjin Medical University General Hospital), Dr Xing Chunyan (Jinan Central Hospital), Dr Dai Yuanrong (The Second Affiliated Hospital of Wenzhou Medical University), Dr Qiu Zhongmin (Tongji Hospital of Tongji University), Dr Zhao Limin (Henan Provincial People's Hospital), Dr Li Feng (Shanghai Chest Hospital), Dr Chang Chun (Peking University Third Hospital), Dr Hu Yi (The Central Hospital of Wuhan), Dr Han Wei (Qingdao Municipal Hospital [Group]), Dr Feng Juntao (Xiangya Hospital Central South University), Dr Su Xinming (The First Hospital of China Medical University), and Dr Zhen Guohua (Tongji Hospital, Tongji Medical College of HUST) for their contribution in patient recruitment, and thank Xiaojun Chen (AstraZeneca China, Medical Affairs) for her contribution in the interpretation of the study results. Medical writing assistance was provided by Syed Abdul Haseeb (MS, CMPP) of Nucleus Global and funded by AstraZeneca, China. Nucleus Global's services complied with international guidelines for Good Publication Practice (GPP3).

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by AstraZeneca. AstraZeneca was involved in the study design, data collection, data analysis, and preparation of the manuscript.

Competing interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: BW, ZY, HJ, GY, TW, YC, DJ, JM, LK, YH, ZX, and ZM declare that they have no competing interests. BM was an employee of AstraZeneca at the time of study conduct.

Availability of data and materials

The data sets used and/or analysed during this study are available from the corresponding author on reasonable request.

ORCID iDs

Kefang Lai https://orcid.org/0000-0001-7994-7296

Min Zhang https://orcid.org/0000-0002-9591-9524

Supplemental material

Supplemental material for this article is available online.

References

1. Huang K, Yang T, Xu J, *et al.* Prevalence, risk factors, and management of asthma in China: a national cross-sectional study. *Lancet* 2019; 394: 407–418.
2. Lai CK, De Guia TS, Kim YY, *et al.* Asthma control in the Asia-Pacific region: the Asthma Insights and Reality in Asia-Pacific Study. *J Allergy Clin Immunol* 2003; 111: 263–268.
3. Mitchell I, Tough SC, Semple LK, *et al.* Near-fatal asthma: a population-based study of risk factors. *Chest* 2002; 121: 1407–1413.
4. Salmeron S, Liard R, Elkharrat D, *et al.* Asthma severity and adequacy of management in accident and emergency departments in France: a prospective study. *Lancet* 2001; 358: 629–635.
5. Global Initiative for Asthma. Global strategy for asthma management and prevention, https://ginasthma.org/archived-reports/ (2018, accessed 30 March 2020).
6. Global Initiative for Asthma. Global strategy for asthma management and prevention, https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf (2019, accessed 30 March 2020).
7. Bateman ED, Reddel HK, O'Byrne PM, *et al.* As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. *N Engl J Med* 2018; 378: 1877–1887.
8. O'Byrne PM, FitzGerald JM, Bateman ED, *et al.* Inhaled combined budesonide-formoterol as needed in mild asthma. *N Engl J Med* 2018; 378: 1865–1876.
9. Patel M, Pilcher J, Pritchard A, *et al.* Efficacy and safety of maintenance and reliever combination

budesonide-formoterol inhaler in patients with asthma at risk of severe exacerbations: a randomised controlled trial. *Lancet Respir Med* 2013; 1: 32–42.

10. Bateman ED, Harrison TW, Quirce S, *et al.* Overall asthma control achieved with budesonide/formoterol maintenance and reliever therapy for patients on different treatment steps. *Respir Res* 2011; 12: 38.
11. Sadatsafavi M, Tavakoli H, Lynd L, *et al.* Has asthma medication use caught up with the evidence? A 12-year population-based study of trends. *Chest* 2017; 151: 612–618.
12. Ding B and Small M. Disease burden of mild asthma in China. *Respirology* 2018; 23: 369–377.
13. Zhong N, Lin J, Zheng J, *et al.* Uncontrolled asthma and its risk factors in adult Chinese asthma patients. *Ther Adv Respir Dis* 2016; 10: 507–517.
14. Cabrera CS, Nan C, Lindarck N, *et al.* SABINA: global programme to evaluate prescriptions and clinical outcomes related to short-acting beta2-agonist use in asthma. *Eur Respir J* 2020; 55: 1901858.
15. Bateman ED, Price DB, Wang HC, *et al.* Short-acting beta2-agonist prescriptions are associated with poor clinical outcomes of asthma: the multi-country, cross-sectional SABINA III study. *Eur Respir J* 2022; 59: 2101402.
16. Bateman ED, Hurd SS, Barnes PJ, *et al.* Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008; 31: 143–178.
17. Pearce N and Hensley MJ. Epidemiologic studies of beta agonists and asthma deaths. *Epidemiol Rev* 1998; 20: 173–186.
18. Spitzer WO, Suissa S, Ernst P, *et al.* The use of beta-agonists and the risk of death and near death from asthma. *N Engl J Med* 1992; 326: 501–506.
19. Thompson PJ, Salvi S, Lin J, *et al.* Insights, attitudes and perceptions about asthma and its treatment: findings from a multinational survey of patients from 8 Asia-Pacific countries and Hong Kong. *Respirology* 2013; 18: 957–967.
20. Janson C, Menzies-Gow A, Nan C, *et al.* SABINA: an overview of short-acting beta2-agonist use in asthma in European countries. *Adv Ther* 2020; 37: 1124–1135.
21. Bloom CI, Cabrera C, Arnetorp S, *et al.* Asthma-related health outcomes associated with short-acting beta2-agonist inhaler use: an observational UK study as part of the SABINA global program. *Adv Ther* 2020; 37: 4190–4208.
22. Nwaru BI, Ekstrom M, Hasvold P, *et al.* Overuse of short-acting beta2-agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. *Eur Respir J* 2020; 55: 1901872.
23. Oppenheimer J, Bogart M, Bengtson LGS, *et al.* Treatment patterns and disease burden associated with multiple-inhaler triple-therapy use in asthma. *J Allergy Clin Immunol Pract* 2022; 10: 485–494.e5.
24. Chauhan BF and Ducharme FM. Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma. *Cochrane Database Syst Rev* 2014; 1: CD003137.
25. Kaplan A, FitzGerald JM, Buhl R, *et al.* Comparing LAMA with LABA and LTRA as add-on therapies in primary care asthma management. *NPJ Prim Care Respir Med* 2020; 30: 50.
26. Di Marco F, D'Amato M, Lombardo FP, *et al.* The burden of short-acting beta2-agonist use in asthma: is there an Italian case? An update from SABINA program. *Adv Ther* 2021; 38: 3816–3830.
27. Worth H, Criee CP, Vogelmeier CF, *et al.* Prevalence of overuse of short-acting beta-2 agonists (SABA) and associated factors among patients with asthma in Germany. *Respir Res* 2021; 22: 108.
28. 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.
29. Suissa S, Ernst P and Kezouh A. Regular use of inhaled corticosteroids and the long term prevention of hospitalisation for asthma. *Thorax* 2002; 57: 880–884.