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Evaluation of short-acting Beta-2-agonist prescriptions and associated clinical outcomes: Findings from the SABA use IN Asthma (SABINA) study in Asia

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ABSTRACT

Background: The extent of short-acting Beta-2-agonist (β_2-agonist) (SABA) use across Asian countries is not well documented. As part of the SABA use IN Asthma (SABINA) III study, we assessed SABA prescriptions and clinical outcomes in patients with asthma from Asia.

Methods: This cross-sectional study recruited patients (aged $\geq$12 years) with asthma from 8 Asian countries. Data on disease characteristics and asthma treatments were collected using electronic case report forms. Patients were classified by practice type (primary or specialist care) and investigator-defined asthma severity (per Global Initiative for Asthma [GINA] 2017 recommendations). The association of SABA prescriptions with clinical outcomes was analyzed using multivariable regression models.

Results: Overall, 3066 patients were analyzed, with a mean (standard deviation) age of 51.8 (16.7) years; of these patients, 2116 (69%) were female, 2517 (82.1%) had moderate-to-severe asthma and 2498 (81.5%) and 559 (18.2%) were treated in specialist and primary care, respectively. In total, 1423 (46.4%) patients had partly controlled/uncontrolled asthma, with 1149 (37.5%) patients experiencing $\geq$1 severe asthma exacerbation in the previous year. Overall, 800 (26.7%) patients were prescribed $\geq$3 SABA canisters in the previous year, which is regarded as overprescription and was associated with a significantly decreased odds of at least partly controlled asthma and increased incidence rates of severe exacerbations ($P < 0.01$ for both associations).

Conclusion: The findings from this cohort of predominantly specialist-treated patients with asthma indicate SABA overprescription in at least 1 in every 4 patients, and this overprescription is associated with poor clinical outcomes. These data highlight the need for adherence to recently updated asthma treatment recommendations in Asia.

Keywords: Asia, Asthma, Prescriptions, Public health, Adrenergic beta-2 receptor agonists

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BACKGROUND

Asthma, primarily driven by airway inflammation, is a major chronic respiratory disease in Asia and globally.[1,2] Although the prevalence of asthma is lower in the Asia-Pacific region (<5%) than in Western countries (≥20%), an upward trend is being observed, potentially as a result of increased urbanization.[1,3] Despite the comparatively lower prevalence observed in Asia, the burden of asthma in this region is substantial and amplified due to underdiagnosis, undertreatment, and inaccessible and/or unaffordable healthcare.[1,4–6]

Although inhaled corticosteroids (ICS) remain the preferred maintenance medication for patients with mild persistent and more severe asthma,[4,7] short-acting Beta-2-agonist (β_2-agonists) (SABAs) have been used for rapid symptom relief. Preclinical and clinical studies have shown that SABAs do not address the underlying airway inflammation[8] but rather increase airway inflammation;[9] therefore, frequent and inappropriate SABA use is associated with increased morbidity, including exacerbations.[10–13] Results from the REcognise Asthma and LInk to Symptoms and Experience (REALISE) Asia, Asthma Insights and Management (AIM), and Asthma Insights and Reality (AIR) surveys reported that less than one-third of patients[14–16] in the Asia-Pacific region used daily maintenance medication, while more than two-thirds of patients[14] used only reliever medication. Overuse of reliever medications and underuse of maintenance ICS medications may thus explain the poor asthma control observed in Asia.[6,14,15,17] Based on growing safety concerns, the latest Global Initiative for Asthma (GINA) recommendations no longer recommend treatment with as-needed SABA without concomitant ICS for symptom relief in patients ≥12 years of age. Instead, low-dose ICS-formoterol is now recommended as the preferred as-needed reliever for adults and adolescents with mild asthma and for those with moderate-to-severe asthma who are prescribed ICS-formoterol maintenance therapy to treat the underlying inflammation and minimize the risk of exacerbations.[4] This recommendation was based on the efficacy of the combination of a low-dose ICS with formoterol, a long-acting β_2-agonist (LABA) with a rapid onset of action in reducing severe exacerbations when compared with SABA monotherapy[18] and ICS maintenance therapy in patients with mild asthma.[19]

Assessment of SABA overuse and its local consequences may help clinicians understand the extent of SABA overuse and its associated risks and advocate for changes in clinical practice in alignment with GINA recommendations. Several studies have established an association between SABA overuse and poor clinical outcomes, in addition to increased healthcare resource utilization.[10,13,20–22] However, similar studies conducted in Asian populations are lacking, with the absence of large healthcare databases acting as a barrier to the conduct of such studies in many Asian countries.

The SABA use IN Asthma (SABINA) program was initiated to describe asthma treatment prescription patterns, the extent of SABA use, and its subsequent impact on asthma-related clinical outcomes through a series of large observational cohort studies using a harmonized approach to data collection, evaluation, and interpretation.[23] Due to the diversity in healthcare systems, the SABINA program comprises 3 main pillars, which share a common objective and design principles from a granular core protocol to ensure scientific alignment: (i) SABINA I, a retrospective, observational database study conducted in the United Kingdom (UK);[24] (ii) SABINA II, a distributed harmonized set of multi-country, retrospective, observational database studies in Canada, France, Germany, Italy, Israel, the Netherlands, Spain, and Sweden;[25–31] and (iii) SABINA III, a multicenter, observational, cross-sectional study in 8351 patients from 24 countries across the Asia-Pacific region,[32–37] Africa,[38–40] the Middle East,[41–44] Latin America,[45–48] and Russia,[49] which used electronic case report forms (eCRFs) to record data from individual patients (patient-level data) and from healthcare providers (HCPs).[50] Overall, results from the United Kingdom and Europe reported that SABA overprescription (or possession of ≥3 canisters/year) is common and associated with poor clinical outcomes.[24,51] Similarly, findings from the SABINA International study (SABINA III) indicated that ≥3 SABA prescriptions per year (vs 1−2 SABA prescriptions) were associated with increasingly lower odds of controlled or partly controlled

asthma and higher rates of severe exacerbations across treatment steps and clinical care settings.[50] Here, we report trends in SABA prescriptions in 8 Asian countries, as a subset of the SABINA III study.

METHODS

Study design

The methodology for SABINA III has been described previously.[50] In brief, this cross-sectional, multi-country, multicenter, observational study was conducted in Malaysia, India, South Korea, Thailand, Taiwan, the Philippines, Indonesia, and Singapore, with patient recruitment from March 2019 to January 2020. Study sites were selected using purposive sampling with the aim of obtaining a sample representative of asthma management within each participating country by a national coordinator. The national coordinator also provided advice on the different types of centers (different types of hospitals and geographical distribution) and facilitated the selection of the investigators. The primary objective was to analyze aggregated data from these 8 countries to describe trends in SABA prescriptions in the asthma patient population. The secondary objectives were to determine the associations between SABA prescriptions and health outcomes. Retrospective baseline data were obtained from existing medical records, while patient data were collected during a single study visit and entered in the eCRF. Physicians entered data on exacerbation history, comorbidities, and information of medication prescriptions for asthma in the eCRF based on patient medical records. Physicians also enquired whether patients had experienced any additional exacerbations that were not documented in their medical records. All study site investigators were trained for using the eCRF system. The study was compliant with the study protocol, local ethics committees, and the Declaration of Helsinki; signed informed consent was obtained from all patients or their legal guardians.

Study population

Patients aged ≥12 years under HCP care who met the following criteria were eligible for enrollment: (i) a documented physician diagnosis of asthma in their medical records; (ii) ≥3 prior HCP consultations with the same HCP or HCP practice; and (iii) medical records containing data for ≥12 months before the study visit. Patients with other chronic respiratory diseases, such as chronic obstructive pulmonary disease, were excluded. Investigators, who were HCPs, were required to select and enroll patients under their care who met the inclusion criteria.

Study variables and outcomes

As described previously,[50] patients were categorized by their SABA canister prescriptions during the 12 months before the study visit. SABA prescriptions were categorized as 0, 1–2, 3–5, 6–9, 10–12, and ≥13 canisters, and overprescription was defined as a prescription of ≥3 SABA canisters in the year prior to the study visit.[23] ICS canister prescriptions were recorded by average daily dose as low, medium, or high based on GINA 2017 recommendations.[7]

Secondary variables included practice type (primary or specialist care), investigator-classified asthma severity (guided by GINA 2017;[7] patients at GINA treatment steps 1–2 were categorized as having mild asthma and patients at steps 3–5 as having moderate-to-severe asthma), asthma treatments in the previous 12 months, and asthma duration. Other variables included healthcare insurance (not reimbursed, partially reimbursed, or fully reimbursed), education level (primary and secondary school, high school, or university and/or post-graduate education), body mass index (BMI), number of comorbidities, and tobacco smoking status. In addition, data for SABA over-the counter (OTC) purchase, which was based on patient recall, was obtained directly from patients at the study visit and entered in the eCRF by the investigator.

The assessed asthma-related health outcomes included asthma symptom control (using the GINA 2017 assessment of asthma control and categorized as well controlled, partly controlled, and uncontrolled) and number of severe asthma exacerbations (defined based on American Thoracic Society/European Respiratory Society recommendations[52] as a deterioration in asthma resulting in hospitalization, emergency room treatment, or the need for intravenous or oral corticosteroids [OCS] for ≥3

days or a single intramuscular corticosteroid dose) in the year before the study.

Statistical analysis

Patient-level analyses are presented as country-aggregated descriptive statistics. A logistic multivariable regression model and a negative binomial regression model were used to analyze the associations of SABA prescriptions with at least partly controlled asthma (partly controlled plus well-controlled asthma, with uncontrolled asthma as the reference) and severe exacerbation incidence rates, respectively. All regression models used a complete-case analysis and were adjusted for prespecified variables (country, age, sex, and smoking status) and potential confounders (asthma severity as classified by investigators, healthcare insurance, education level, comorbidities, duration of asthma, and BMI). Patients with 0 SABA prescriptions were excluded from the secondary analyses because alternative relievers used by such patients were not recorded. The Kendall correlation test was used to assess the correlation between prescriptions of ICS and prescriptions of SABAs in addition to maintenance therapy. All statistical tests were 2-sided at a 5% level of significance and performed using R statistical software (version 3.6.0).

RESULTS

Of the 3125 patients enrolled, 59 were excluded because their asthma duration was <12 months (Fig. 1). Most patients were recruited from Malaysia (n = 732; 23.9%), followed by India (n = 510; 16.6%) and South Korea (n = 476; 15.5%; Fig. 2).

Most patients were treated by specialists (81.5%), whereas 18.2% of patients were treated in primary care (Fig. 1). Overall, 82.1% of patients had moderate-to-severe asthma (GINA steps 3–5). Patients had a mean (standard deviation [SD]) age of 51.8 (16.7) years, and most were female (69.0%; Table 1). Over half of all patients were obese (n = 1702 [55.5%]) according to the Asia-Pacific body mass index classification,[53] and most had no history of smoking (n = 2591 [84.5%]). Over one-fourth of all patients had received primary/secondary school education (37.9%) and university and/or post-graduate education (30.2%). Similar findings were observed in both primary and specialist care. Additionally, almost one-fourth (21.4%) of patients did not have reimbursed healthcare. Most patients had 0 (32.0%) or 1–2 (49.2%) comorbidities. Patients experienced a mean (SD) of 0.84 (1.82) severe asthma exacerbations in the year before the study, and 37.5%

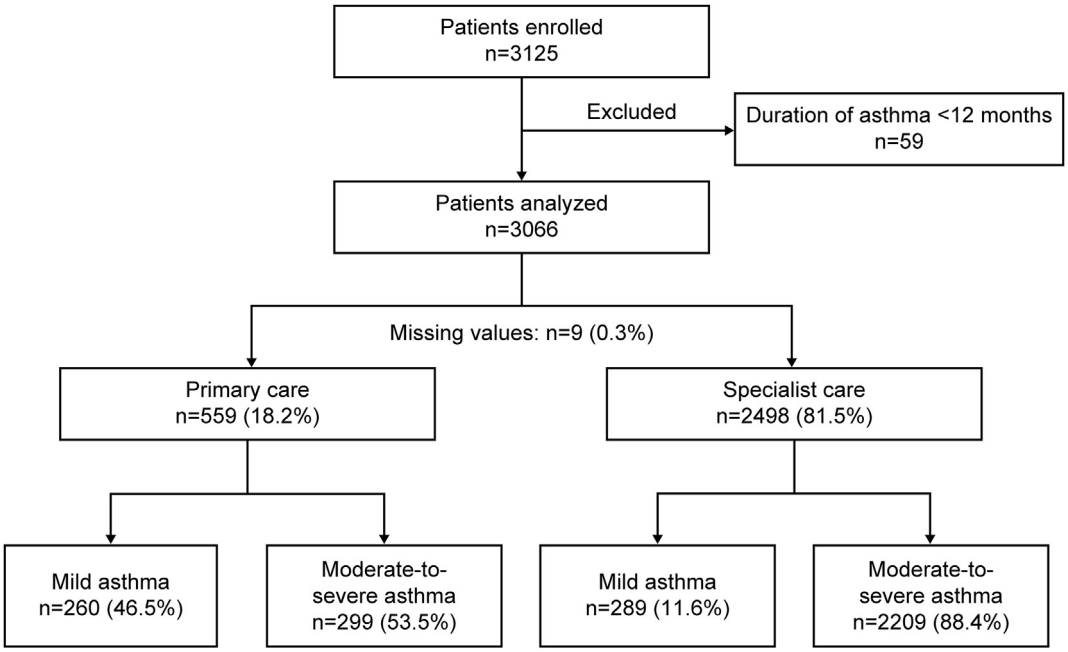

Fig. 1 Patient disposition and study population by practice type and investigator-classified asthma severity

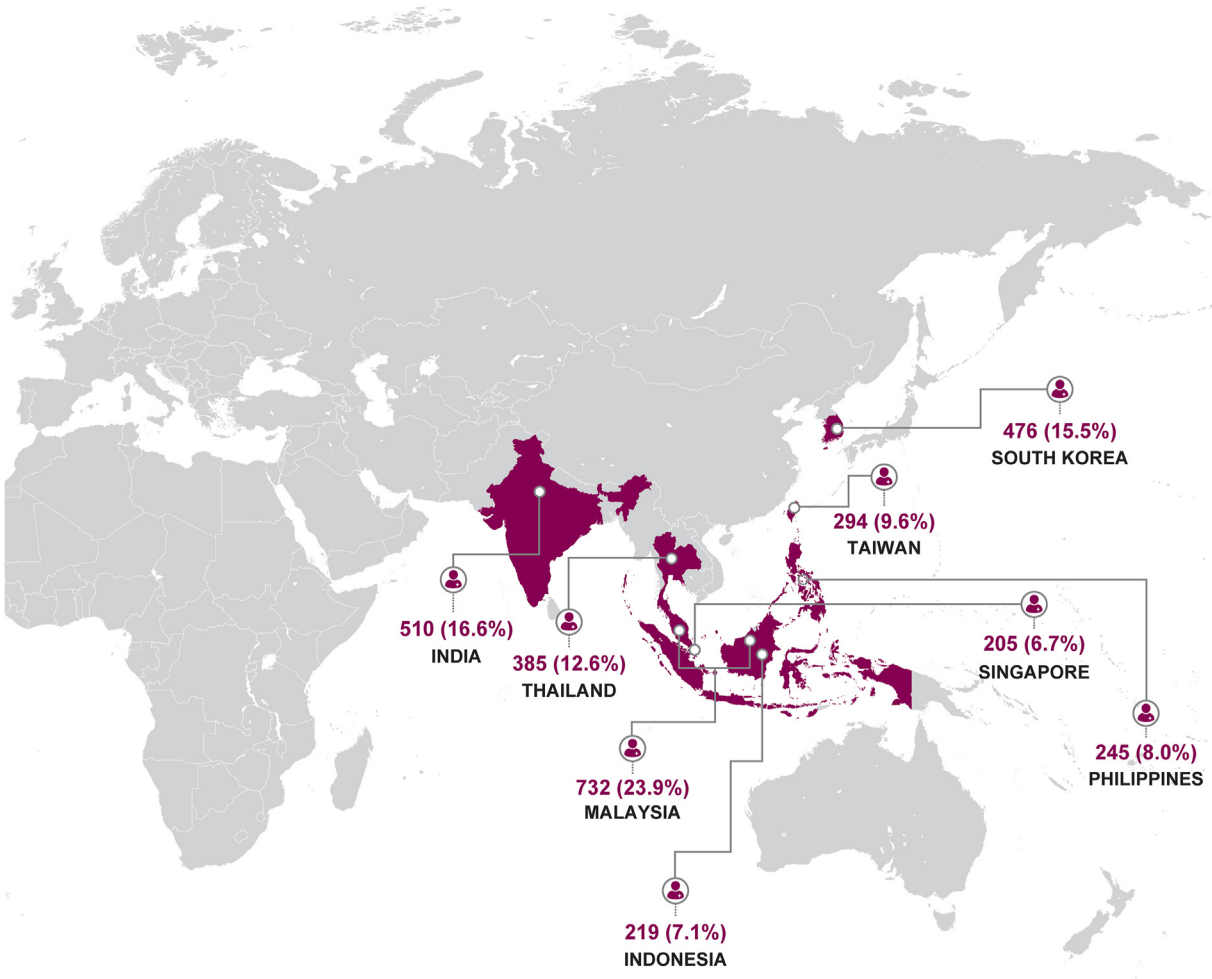

Fig. 2 Patient enrollment across countries in the SABINA III Asian cohort

experienced ≥1 severe asthma exacerbation (Table 2). Over half of all patients (53.6%) had well-controlled asthma, 29.4% had partly controlled asthma, and 17.1% had uncontrolled asthma across severities.

Asthma treatment in the 12 months before the study visit

Overall, 26.7% of patients were prescribed ≥3 SABA canisters in the previous 12 months (Fig. 3). Similar results were observed across severities, with 30.5% and 25.8% of patients with mild and moderate-to-severe asthma, respectively, being prescribed ≥3 canisters.

SABA monotherapy

Only 2.9% of patients were prescribed SABA monotherapy, with a mean (SD) of 4.0 (4.6) canisters (Table 3). Among these patients, 41.2% were prescribed ≥3 canisters, and 15.3% were prescribed ≥10 canisters. Among patients with mild asthma who were prescribed SABA monotherapy, 42.9% and 38.1% were prescribed ≥3 SABA canisters under primary and specialist care, respectively.

SABA plus maintenance therapy

Over half (52.0%) of all patients were prescribed SABA in addition to maintenance therapy, with a mean (SD) of 5.1 (10.6) canisters (Table 3). Overall,

Demographic and lifestyle characteristics	All (N = 3066)[a]	Primary care (n = 559)			Specialists (n = 2498)		
		Investigator-classified mild asthma (n = 260)	Investigator-classified moderate-to-severe asthma (n = 299)	All (n = 559)	Investigator-classified mild asthma (n = 289)	Investigator-classified moderate-to-severe asthma (n = 2209)	All (n = 2498)
Age (years)							
Mean (SD)	51.8 (16.7)	46.2 (16.8)	50.1 (16.3)	48.3 (16.6)	45.5 (19.9)	53.5 (15.9)	52.6 (16.6)
Range	12.0–92.0	12.0–81.0	15.0–91.0	12.0–91.0	12.0–88.0	12.0–92.0	12.0–92.0
Age groups (years)							
12–17	87 (2.8)	24 (9.2)	3 (1.0)	27 (4.8)	40 (13.8)	20 (0.9)	60 (2.4)
18–54	1515 (49.4)	137 (52.7)	180 (60.2)	317 (56.7)	141 (48.8)	1052 (47.6)	1193 (47.8)
≥55	1464 (47.7)	99 (38.1)	116 (38.8)	215 (38.5)	108 (37.4)	1137 (51.5)	1245 (49.8)
Sex							
Female	2116 (69.0)	191 (73.5)	211 (70.6)	402 (71.9)	191 (66.1)	1516 (68.6)	1707 (68.3)
Male	950 (31.0)	69 (26.5)	88 (29.4)	157 (28.1)	98 (33.9)	693 (31.4)	791 (31.7)
BMI (kg/m^2)							
Mean (SD)	26.3 (5.6)	27.2 (6.0)	26.5 (6.1)	26.8 (6.1)	25.6 (5.7)	26.3 (5.4)	26.2 (5.5)
Median (min, max)	25.5 (12.6, 71.3)	26.5 (12.6, 49.7)	25.4 (16.6, 52.5)	25.8 (12.6, 52.5)	25.0 (14.9, 58.7)	25.5 (14.2, 71.3)	25.5 (14.2, 71.3)
BMI groups[b] (kg/m^2)							
<18.5	127 (4.1)	NA	NA	NA	NA	NA	NA
18.5–22.9	716 (23.4)	NA	NA	NA	NA	NA	NA
23–24.9	521 (17.0)	NA	NA	NA	NA	NA	NA
≥25	1702 (55.5)	NA	NA	NA	NA	NA	NA

Education level							
Not established	302 (9.8)	8 (3.1)	28 (9.4)	36 (6.4)	19 (6.6)	245 (11.1)	264 (10.6)
Primary or secondary school	1162 (37.9)	149 (57.3)	116 (38.8)	265 (47.4)	96 (33.2)	798 (36.1)	894 (35.8)
High school	675 (22.0)	51 (19.6)	51 (17.1)	102 (18.2)	90 (31.1)	481 (21.8)	571 (22.9)
University and/or post-graduate education	927 (30.2)	52 (20.0)	104 (34.8)	156 (27.9)	84 (29.1)	685 (31.0)	769 (30.8)
Healthcare insurance/medication funding							
Not reimbursed	655 (21.4)	42 (16.2)	53 (17.7)	95 (17.0)	78 (27.0)	481 (21.8)	559 (22.4)
Partially reimbursed	775 (25.3)	17 (6.5)	107 (35.8)	124 (22.2)	78 (27.0)	568 (25.7)	646 (25.9)
Fully reimbursed	1469 (47.9)	194 (74.6)	118 (39.5)	312 (55.8)	127 (43.9)	1027 (46.5)	1154 (46.2)
Unknown	167 (5.4)	8 (3.1)	28 (9.4)	36 (6.4)	19 (6.6)	245 (11.1)	264 (10.6)
Smoking status							
Active smoker	126 (4.1)	11 (4.2)	20 (6.7)	31 (5.5)	7 (2.4)	88 (4.0)	95 (3.8)
Former smoker	349 (11.4)	23 (8.8)	36 (12.0)	59 (10.6)	25 (8.7)	265 (12.0)	290 (11.6)
Never smoker	2591 (84.5)	226 (86.9)	243 (81.3)	469 (83.9)	257 (88.9)	1856 (84.0)	2113 (84.6)
Number of comorbidities							
0	981 (32.0)	94 (36.2)	112 (37.5)	206 (36.9)	103 (35.6)	670 (30.3)	773 (30.9)
1–2	1508 (49.2)	126 (48.5)	111 (37.1)	237 (42.4)	147 (50.9)	1118 (50.6)	1265 (50.6)
3–4	455 (14.8)	39 (15.0)	60 (20.1)	99 (17.7)	33 (11.4)	323 (14.6)	356 (14.3)
≥5	122 (4.0)	1 (0.4)	16 (5.4)	17 (3.0)	6 (2.1)	98 (4.4)	104 (4.2)

Table 1. Demographic and lifestyle characteristics by investigator-classified asthma severity and practice type. *BMI, body mass index; max, maximum; min, minimum; NA, not available; SD, standard deviation, WHO, World Health Organization. Data are presented as n (%) unless otherwise specified.* [a]*Practice type was not recorded for 9 patients.* [b]*According to Asia-Pacific BMI classification. The Asia-Pacific BMI classification data were available for the broad BMI categories; however, the stratification by practice type was only available as per the WHO classification. Therefore, all fields under practice type are marked as NA*

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Asthma-related clinical characteristics	All (N = 3066)[a]	Primary care (n = 559)			Specialists (n = 2498)		
		Investigator-classified mild asthma (n = 260)	Investigator-classified moderate-to-severe asthma (n = 299)	All (n = 559)	Investigator-classified mild asthma (n = 289)	Investigator-classified moderate-to-severe asthma (n = 2209)	All (n = 2498)
Asthma duration (years)							
Mean (SD)	14.1 (14.5)	21.46 (16.0)	15.82 (14.5)	18.44 (15.5)	12.43 (13.6)	13.23 (14.2)	13.13 (14.1)
Median (min, max)	9.0 (1.0, 83.0)	17.0 (1.0, 68.0)	11.0 (1.0, 65.0)	13.0 (1.0, 68.0)	8.0 (1.0, 65.0)	8.0 (1.0, 83.0)	8.0 (1.0, 83.0)
Number of severe asthma exacerbations 12 months before the study visit							
Mean (SD)	0.84 (1.8)	0.93 (2.2)	0.86 (1.6)	0.89 (1.9)	0.38 (1.2)	0.89 (1.9)	0.83 (1.8)
Number of severe asthma exacerbations 12 months before the study visit by group							
0	1917 (62.5)	156 (60.0)	186 (62.2)	342 (61.2)	237 (82.0)	1333 (60.3)	1570 (62.9)
1	585 (19.1)	52 (20.0)	54 (18.1)	106 (19.0)	26 (9.0)	452 (20.5)	478 (19.1)
2	241 (7.9)	19 (7.3)	27 (9.0)	46 (8.2)	12 (4.2)	181 (8.2)	193 (7.7)
3	151 (4.9)	21 (8.1)	14 (4.7)	35 (6.3)	8 (2.8)	108 (4.9)	116 (4.6)
>3	172 (5.6)	12 (4.6)	18 (6.0)	30 (5.4)	6 (2.1)	135 (6.1)	141 (5.6)
GINA classification							
Step 1	205 (6.7)	98 (37.7)	0 (0.0)	98 (17.5)	107 (37.0)	0 (0.0)	107 (4.3)
Step 2	344 (11.2)	162 (62.3)	0 (0.0)	162 (29.0)	182 (63.0)	0 (0.0)	182 (7.3)
Step 3	1003 (32.7)	0 (0.0)	166 (55.5)	166 (29.7)	0 (0.0)	834 (37.8)	834 (33.4)
Step 4	1234 (40.2)	0 (0.0)	119 (39.8)	119 (21.3)	0 (0.0)	1109 (50.2)	1109 (44.4)
Step 5	280 (9.1)	0 (0.0)	14 (4.7)	14 (2.5)	0 (0.0)	266 (12.0)	266 (10.6)

Level of asthma control							
Well controlled	1643 (53.6)	146 (56.2)	134 (44.8)	280 (50.1)	203 (70.2)	1156 (52.3)	1359 (54.4)
Partly controlled	900 (29.4)	67 (25.8)	121 (40.5)	188 (33.6)	63 (21.8)	646 (29.2)	709 (28.4)
Uncontrolled	523 (17.1)	47 (18.1)	44 (14.7)	91 (16.3)	23 (8.0)	407 (18.4)	430 (17.2)

Table 2. Asthma-related clinical characteristics. *GINA, Global Initiative for Asthma; max, maximum; min, minimum; SD, standard deviation. Data are presented as n (%) unless otherwise specified.* [a]*Practice type was not recorded for 9 patients*

50% of patients who were prescribed SABA in addition to maintenance therapy were prescribed ≥3 SABA canisters, and 12.3% were prescribed ≥10 SABA canisters. A similar proportion of patients were prescribed ≥3 canisters in primary and specialist care (44.7% and 51.0%, respectively) across severities.

Other SABA prescriptions

Altogether, 2.7% and 7.3% of all patients were prescribed oral and nebulized forms of SABA, respectively (Table 3).

Over-the-counter SABA

Overall, 7.7% of patients purchased SABA OTC (Supplementary Table 1) of whom 32.8% purchased ≥3 canisters. Patients treated in primary care had greater SABA purchases than patients in specialist care across severities (12.3% vs 6.7%). Notably, 33.9% and 38.6% of patients who purchased SABA OTC had partly controlled and uncontrolled asthma, respectively (Supplementary Table 2).

Other prescriptions of asthma medications in the 12 months before the study visit

Overall, 14.0% of patients were prescribed maintenance ICS monotherapy, with a mean (SD) of 5.1 (11.5) ICS canisters (Supplementary Table 3) Most patients were prescribed low-dose (43.7%) or medium-dose (50.8%) ICS. Almost one-third (32.4%) of patients were prescribed ICS monotherapy in primary care, 86.2% of whom had mild asthma. In contrast, only 9.9% of patients in specialist care were prescribed ICS monotherapy.

Overall, 84.2% of patients were prescribed ICS/LABA fixed-dose combinations, with 39.0% receiving low-dose ICS and 49.8% receiving medium-dose ICS (Supplementary Table 3). Most patients with moderate-to-severe asthma in primary and specialist care were prescribed ICS/LABA; however, 5.8% and 26.6% of patients with mild asthma in primary and specialist care, respectively, also had ICS/LABA prescriptions.

OCS bursts were prescribed to 29.7% of patients, with comparable findings in primary and specialist care (Supplementary Table 3). In addition, 7.8% of patients were prescribed OCS maintenance doses and 19.1% were prescribed

SABA prescriptions in the previous 12 months	All (N = 3066)[a]	Primary care (n = 559)			Specialists (n = 2498)		
		Investigator-classified mild asthma (n = 260)	Investigator-classified moderate-to-severe asthma (n = 299)	All (n = 559)	Investigator-classified mild asthma (n = 289)	Investigator-classified moderate-to-severe asthma (n = 2209)	All (n = 2498)
Number of patients prescribed inhaled SABA monotherapy							
Yes	89 (2.9)	45 (17.3)	0 (0.0)	45 (8.1)	43 (14.9)	1 (0.0)	44 (1.8)
No	2977 (97.1)	215 (82.7)	299 (100)	514 (91.9)	246 (85.1)	2208 (100)	2454 (98.2)
Number of canisters/inhalers prescribed per patient 12 months before the study visit							
n	85	42	NA	42	42	1	43
Mean (SD)	4.0 (4.6)	5.0 (5.6)	NA	5.0 (5.6)	3.1 (3.1)	3.0 (NA)	3.1 (3.0)
Median (min, max)	2.0 (1.0, 16.0)	2.0 (1.0, 16.0)	NA	2.0 (1.0, 16.0)	2.0 (1.0, 12.0)	3.0 (3.0, 3.0)	2.0 (1.0, 12.0)
Missing data	4 (4.5)	3 (6.7)	NA	3 (6.7)	1 (2.3)	0 (0.0)	1 (2.3)
Number of canisters/inhalers prescribed per patient 12 months before the study visit by category							
1–2	50 (58.8)	24 (57.1)	NA	24 (57.1)	26 (61.9)	0 (0.0)	26 (60.5)
3–5	18 (21.2)	5 (11.9)	NA	5 (11.9)	12 (28.6)	1 (100)	13 (30.2)
6–9	4 (4.7)	4 (9.5)	NA	4 (9.5)	0 (0.0)	0 (0.0)	0 (0.0)
10–12	6 (7.1)	2 (4.8)	NA	2 (4.8)	4 (9.5)	0 (0.0)	4 (9.3)
≥13	7 (8.2)	7 (16.7)	NA	7 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Missing data (n)	4	3	NA	3	1	0	1
Total	85	42	NA	42	42	1	43
Number of patients prescribed inhaled SABA in addition to maintenance therapy							
Yes	1594 (52.0)	157 (60.4)	138 (46.2)	295 (52.8)	129 (44.6)	1169 (52.9)	1298 (52)
No	1472 (48.0)	103 (39.6)	161 (53.8)	264 (47.2)	160 (55.4)	1040 (47.1)	1200 (48)

Number of canisters/inhalers prescribed per patient 12 months before the study visit							
n	1531	156	110	266	126	1138	1264
Mean (SD)	5.1 (10.6)	4.6 (4.7)	5.1 (20.1)	4.8 (13.4)	2.9 (2.8)	5.4 (10.4)	5.1 (10.0)
Median (min, max)	2.0 (1.0, 210.0)	3.0 (1.0, 18.0)	2.0 (1.0, 210.0)	2.0 (1.0, 210.0)	2.0 (1.0, 16.0)	3.0 (1.0, 196.0)	3.0 (1.0, 196.0)
Missing data	63 (4.0)	1 (0.6)	28 (20.3)	29 (9.8)	3 (2.3)	31 (2.7)	34 (2.6)
Number of canisters/inhalers prescribed per patient 12 months before the study visit by category							
1–2	766 (50.0)	76 (48.7)	71 (64.5)	147 (55.3)	75 (59.5)	544 (47.8)	619 (49.0)
3–5	377 (24.6)	37 (23.7)	21 (19.1)	58 (21.8)	35 (27.8)	283 (24.9)	318 (25.2)
6–9	199 (13.0)	18 (11.5)	7 (6.4)	25 (9.4)	10 (7.9)	164 (14.4)	174 (13.8)
10–12	106 (6.9)	11 (7.1)	5 (4.5)	16 (6.0)	5 (4.0)	85 (7.5)	90 (7.1)
≥13	83 (5.4)	14 (9.0)	6 (5.5)	20 (7.5)	1 (0.8)	62 (5.4)	63 (5.0)
Missing data (n)	63	1	28	29	3	31	34
Total	1531	156	110	266	126	1138	1264
Number of patients prescribed oral SABA							
Yes	83 (2.7)	13 (5.0)	12 (4.0)	25 (4.5)	5 (1.7)	53 (2.4)	58 (2.3)
No	2983 (97.3)	247 (95.0)	287 (96.0)	534 (95.5)	284 (98.3)	2156 (97.6)	2440 (97.7)
Number of patients prescribed nebulized SABA							
Yes	224 (7.3)	80 (30.8)	51 (17.1)	131 (23.4)	20 (6.9)	73 (3.3)	93 (3.7)
No	2842 (92.7)	180 (69.2)	248 (82.9)	428 (76.6)	269 (93.1)	2136 (96.7)	2405 (96.3)

Table 3. SABA prescriptions in the 12 months before the study visit. *Max, maximum; min, minimum; NA, not available; SABA, short-acting β_2-agonist; SD, standard deviation. Data are presented as n (%) unless otherwise specified. Missing data are not included in the calculation of percentages. [a]Practice type was not recorded for 9 patients*

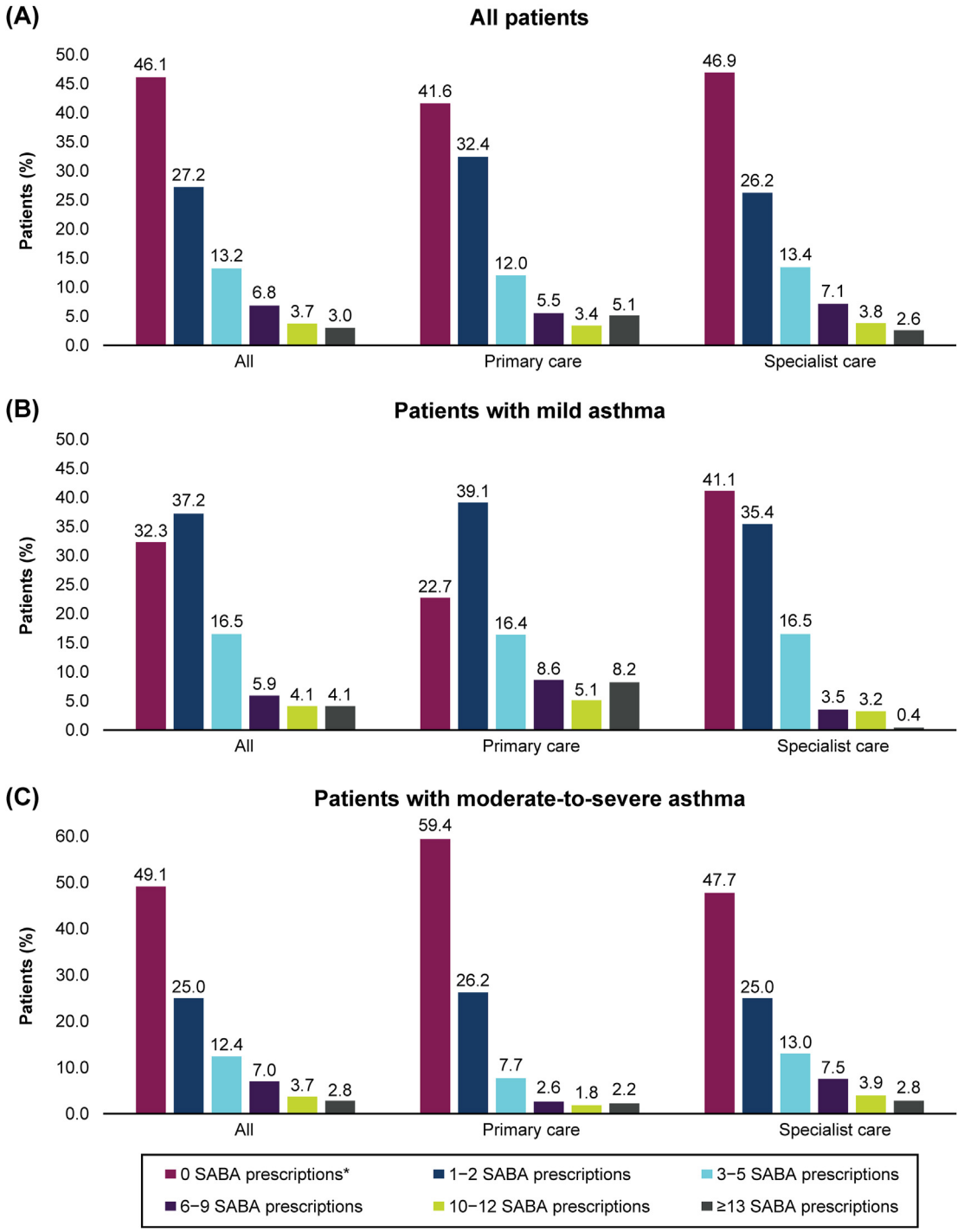

Fig. 3 SABA prescriptions according to investigator-classified asthma severity and practice type. SABA, short-acting β_2-agonist

antibiotics for their asthma (Supplementary Table 4).

Overall, 25.8%, 42.9%, and 38.6% of patients who were prescribed SABA monotherapy, ICS, and ICS/LABA fixed-dose combinations, respectively, had experienced ≥1 severe asthma exacerbation (Table 4). Notably, 20.8% of patients who were prescribed short-course OCS had never experienced a severe asthma exacerbation.

	All (N = 3066)	SABA mono (n = 89)	SABA as an add-on (n = 1594)	ICS mono (n = 429)	ICS/LABA (fixed dose) (n = 2581)	OCS short course (n = 910)
Number of severe exacerbations 12 months before the study visit, n (%)						
0	1917 (62.5)	66 (74.2)	869 (54.5)	245 (57.1)	1584 (61.4)	189 (20.8)
1	585 (19.1)	14 (15.7)	364 (22.8)	81 (18.9)	514 (19.9)	333 (36.6)
2	241 (7.9)	2 (2.2)	162 (10.2)	48 (11.2)	209 (8.1)	145 (15.9)
3	151 (4.9)	5 (5.6)	81 (5.1)	32 (7.5)	120 (4.6)	110 (12.1)
4	66 (2.2)	1 (1.1)	38 (2.4)	8 (1.9)	60 (2.3)	50 (5.5)
5	40 (1.3)	1 (1.1)	26 (1.6)	3 (0.7)	36 (1.4)	28 (3.1)
>5	66 (2.2)	0 (0.0)	54 (3.4)	12 (2.8)	58 (2.2)	55 (6.0)
Total (n)	3066	89	1594	429	2581	910

Table 4. Number of severe exacerbations and treatments in the 12 months before the study visit. *ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist; mono, monotherapy; OCS, oral corticosteroids; SABA, short-acting β_2-agonist*

Factors associated with SABA overprescription

In a post hoc analysis conducted to determine the association between ICS and SABA prescriptions in addition to maintenance therapy, patients with a high number of ICS prescriptions received significantly more SABA prescriptions (data not shown; Kendall correlation coefficient, 0.18; $P < 0.001$).

Association of SABA prescriptions with asthma-related outcomes

In prespecified regression analyses (Supplementary Figure 1), prescriptions of ≥3 SABA canisters (vs 1–2 canisters) were associated with an increase in the incidence rate of severe exacerbations ($P < 0.05$; Fig. 4). Additionally, higher SABA prescriptions (≥3 canisters) were associated with a significantly decreased odds of having at least partly controlled asthma vs 1–2 canisters ($P < 0.01$; Fig. 4).

Comparison of results between SABINA Asia and SABINA III

A comparison of data on sociodemographic and clinical characteristics, asthma treatments, and asthma-related clinical outcomes in the previous 12 months between the SABINA Asia cohort and the overall SABINA III population is summarized in Supplementary Table 5. The key differences are highlighted in the Discussion section.

DISCUSSION

This Pan-Asian study conducted in >3000 patients with asthma demonstrated that ≥3 SABA canisters were prescribed to 26% of patients in the 12 months before the study visit. Most patients (98.2%) were prescribed maintenance therapy in the form of either ICS or ICS/LABA fixed-dose combination therapy; furthermore, OCS burst treatment was prescribed to 29.7% of patients, potentially for the management of worsening asthma symptoms and/or to treat severe exacerbations.[4] Notably, SABA overprescription significantly increased the odds of uncontrolled asthma and severe exacerbation incidence rates.

The patient and disease characteristics and key results of this study are generally consistent with the global trends observed in the SABINA III study.[50] However, compared with the overall SABINA III population (mean age, 49.4 years),[50] patients in this Asian cohort were slightly older (mean age, 51.8 years); this is in line with previous studies that have reported increasing asthma prevalence with age in Asian populations, including those from South Korea,[54] China,[55] Taiwan,[56] and India.[57,58] Moreover, in

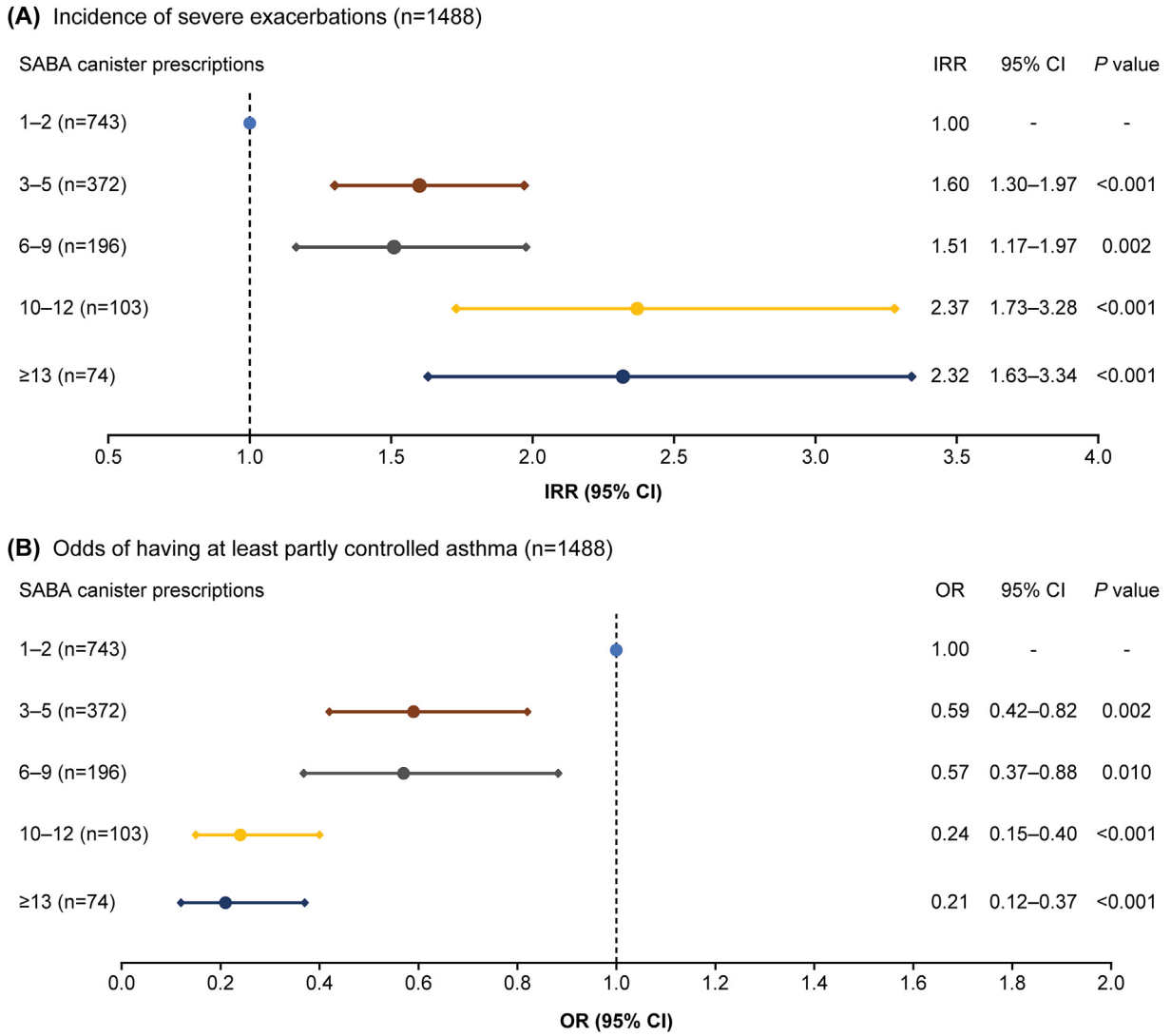

Fig. 4 Association of SABA prescriptions with (A) severe exacerbations and (B) level of asthma symptom control. BMI, body mass index; CI, confidence interval; GINA, Global Initiative for Asthma; IRR, incidence rate ratio; OR, odds ratio; SABA, short-acting β_2-agonist

accordance with increasing evidence that older females with a high BMI represent a distinct asthma phenotype,[59,60] the majority of patients in this Asian cohort were female (69%) and classified as obese (55%; BMI ≥25 kg/m^2). Interestingly, despite older age and high BMI being associated with poorer disease control,[61,62] compared with the overall SABINA III population, a higher proportion of patients from Asia had well-controlled asthma (53.6% vs 43.3%), with a lower proportion experiencing ≥1 severe asthma exacerbation in the preceding 12 months (37.5% vs 45.4%).[50] Such findings may be attributable to the fact that a lower proportion of patients in this Asian cohort were overprescribed SABA treatments compared with the SABINA III study (26.0% vs 38.0%).[50] Moreover, most patients in this Pan-Asian study were treated by specialists who are likely more familiar with current asthma treatment guidelines.

Overall, findings from Asia are also consistent with those from the SABINA I/II studies, where over one-third of patients were overprescribed SABA across 5 countries in Europe.[51] However, only 7.7% of patients in this Asian cohort purchased SABA OTC, potentially reflecting the fact that SABA purchase is illegal in Taiwan and strictly regulated in Singapore. A higher proportion of patients with OTC SABA purchases had partly controlled or uncontrolled asthma compared with those in the overall SABINA Asia cohort (72.5%

vs 17.1%), suggesting that poor asthma control resulted in SABA purchase. However, 27.5% of patients with OTC SABA purchases had well-controlled asthma, potentially indicating unnecessary SABA use in some patients. Cumulatively, our results suggest that high SABA prescriptions are a potential public health risk across Asia and should be closely monitored, together with OTC SABA purchase, to identify patients at risk of poor asthma-related outcomes. In our study, almost half of all patients were not prescribed any inhaled SABA. While a proportion of these patients may have had well-controlled asthma or purchased SABA OTC, over 20% of patients used oral or nebulized SABA as a reliever. For instance, in the Philippines, oral/nebulized SABA is commonly used and available for purchase even without prescriptions. Oral SABA use in low-resource settings in Asian countries can be attributed to a preference for oral medications, together with treatment affordability issues.[63-66] While the use of low-dose ICS-formoterol as maintenance and reliever therapy (MART) was not recorded in the study, the use of MART by patients with moderate-to-severe asthma cannot be discounted.

Among patients with mild asthma who had received ICS maintenance therapy, >60% were prescribed medium-to-high doses of ICS in the previous 12 months. While ICS/LABA could have been prescribed to some patients with mild asthma as anti-inflammatory reliever therapy for as-needed use in alignment with GINA recommendations, some prescriptions in primary care could also be attributed to the unfamiliarity of primary care physicians with GINA recommendations[67] or local guidelines recommending low-dose ICS/LABA instead of ICS monotherapy for mild asthma, such as in the Philippines. Additionally, results of the Kendall correlation test demonstrated that patients with a high number of ICS prescriptions received significantly more SABA prescriptions (correlation coefficient, 0.18; $P < 0.001$). This is consistent with findings from a study analyzing administrative claims data from 38,538 patients with persistent asthma, which also reported that patients receiving ICS monotherapy were more likely to use SABAs, compared with those prescribed ICS/LABA fixed-dose combination therapy.[68] These observations may be explained by the fact that ICS/LABA fixed-dose combination therapy has been shown to be more effective than ICS monotherapy in relieving asthma symptoms, improving lung function and reducing SABA use.[69] Indeed, in this Asian cohort, a higher proportion of patients prescribed ICS monotherapy compared with those prescribed an ICS/LABA fixed-dose combination experienced ≥1 severe asthma exacerbation (42.9% vs 38.6%).

To date, only a few studies have been conducted in patients with asthma in Asia.[14,16,70] Moreover, no study has focused specifically on SABA prescriptions. To the best of our knowledge, this is the first study assessing trends in SABA overprescription and their implications for patient health status in Asia. The results are in agreement with those of global studies demonstrating an association between SABA overuse and frequent exacerbations[12,24,28,71] and poor asthma symptom control.[20] Taken together, our study underscores the need for educational initiatives targeting patients, pharmacists, and physicians to reduce SABA overreliance and improve outcomes through adherence to local and international recommendations.

More than 80% of patients in our cohort had moderate-to-severe asthma (GINA steps 3–5), probably because most patients were treated by specialists. Restricted accessibility to primary care clinics and country-specific regulatory roadblocks limited recruitment by primary care physicians, which would have provided a more complete overview of real-world practice in Asian countries.[72] Based on medical records, >98% of patients in SABINA Asia received maintenance medication. In contrast, self-reported use of daily asthma controller medication ranged from 13.9% in the REALISE Asia study[15] to 32% in the AIM survey in the Asia-Pacific region, indicating suboptimal use of maintenance medication.[14] The level of asthma symptom control was also greater in our study, as >80% of patients had either well-controlled or partly controlled asthma vs 50.3% in the REALISE Asia study.[15] Over 60% of patients in our cohort did not experience any severe exacerbation in the previous 12 months, whereas >60% of patients in the Asia-Pacific region in the AIR survey reported severe exacerbations.[16] In addition, over two-thirds of patients had partial or full healthcare reimbursement, which may not

necessarily reflect the true healthcare landscape in Asia. For example, Taiwan offers fully reimbursed healthcare,[73] while healthcare expenditures are largely out-of-pocket in India.[74] Collectively, this Asian cohort may represent a "better-case scenario" with respect to disease characteristics, sociodemographic parameters, and access to healthcare in these countries. Nonetheless, excessive SABA prescriptions were common, suggesting that the clinical scenario could be considerably worse in these Asian countries than that observed in our study. However, overall, the results should be interpreted in the context of country-specific clinical practices and regulations, which will be discussed in separate publications describing country-specific findings.

Some limitations of this multi-country study should be considered. For instance, as data input into the eCRF relied on physicians, misinterpretation of instructions and possible erroneous classification of asthma severity or practice type may have affected the findings. The use of prescription data may not always reflect actual use, and predominantly specialist-acquired data from Asia may have limited generalizability. Additionally, asthma severity is a strong independent risk factor for future exacerbations;[75] therefore, the fact that over 80% of patients in this study were classified with moderate-to-severe asthma, may have increased exacerbation rates, thereby further limiting the generalizability of our findings. This study also used purposive sampling which may be prone to research bias. Finally, this study only recorded the number of comorbidities (categorized as 0, 1–2, 3–4, and $\geq$5) in the eCRF, while data on the type and rate of comorbidities, which may have impacted the patient outcomes, were not collected. However, aggregated data from these 8 Asian countries enabled the analysis of a large patient population reflective of real-world diagnosis, treatment, and follow-up practices across Asia. Moreover, the standardized threshold used for determining SABA overprescription allowed for a direct comparison with global data.

CONCLUSIONS

This large observational study conducted across 8 Asian countries identified SABA overprescription in more than one-quarter of patients with asthma in this predominantly specialist-treated cohort. Considering the safety concerns associated with SABA overuse, these results highlight a potential public health concern, indicating the need for HCPs and policymakers to work together to ensure that clinical practices in Asia are aligned with the latest evidence-based treatment guidelines.

Abbreviations

AIM, Asia Asthma Insights and Management; AIR, Asthma Insights and Reality; BMI, body mass index; CI, confidence interval; eCRF, electronic case report form; GINA, Global Initiative for Asthma; IRR, incidence rate ratio; HCP, healthcare provider; ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist; MART, maintenance and reliever therapy; NA, not available; OCS, oral corticosteroids; OR, odds ratio; OTC, over the counter; REALISE, REcognise Asthma and LInk to Symptoms and Experience; SABINA, SABA use IN Asthma; SD, standard deviation; SABA, short-acting β_2-agonist.

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Availability of data and materials

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Authors' contributions

MJHIB contributed to conceptualization, methodology, supervision, and visualization efforts. LY supported supervision efforts. HC-W, SD, LS, TT, HFL, HFY, and ABYL contributed equally to investigation efforts. All authors contributed equally to writing, review, and editing of the manuscript.

Ethics approval and consent to participate

The study was compliant with the study protocol, local ethics committees, and the Declaration of Helsinki; signed informed consent was obtained from all patients or their legal guardians. Because patients were only queried as

aggregates and no protected, identifiable health information was available for queries, no institutional review board approval was required for the use of this database or the completion of this study.

Authors' consent for publication

All authors agree to publish this work. All authors confirm and agree to the editorial policy. Authors confirm that their manuscript is original, has not been published before, is not currently being considered for publication elsewhere, and has not been posted to a preprint server.

Competing interest

H-CW, LS, TT, HFL, and ABY-L report no disclosures. SD has received honoraria for educational activities from and served on the advisory boards of AstraZeneca, Novartis, Boehringer Ingelheim, and Zambon. KHY is a member of the advisory boards of GlaxoSmithKline, AstraZeneca, Boehringer Ingelheim, Novartis Healthcare, Takeda Healthcare, Nycomed, Teva, MSD, Mundipharma, Hyundai, and Ankook. DVD is a member of the Advisory Boards and/or Speakers' Bureau and has received honoraria/lecture fees from AstraZeneca, Boehringer-Ingelheim, Cathay Drug Co. Inc., Getz Pharma, GlaxoSmithKline, Glenmark, Johnson & Johnson, Multicare Pharmaceuticals, Mundipharma, Novartis Healthcare, Orient EuroPharma, Pfizer, Takeda Healthcare, Unilab, and Westmont Pharmaceuticals, Inc.; DVD has also received honoraria as Principal Investigator in clinical trials sponsored by AstraZeneca, GlaxoSmithKline, Johnson & Johnson, Novartis Healthcare, and Takeda Healthcare. MJHIB was an employee of AstraZeneca at the time of study conduct and manuscript development. LY is an employee of AstraZeneca.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2023.100823.

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