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ORIGINAL ARTICLE

Short-acting β_2-agonist prescription patterns and clinical outcomes in Malaysia: A nationwide cohort of the SABINA III study

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Abstract

Introduction: SABINA III assessed short-acting β_2-agonist (SABA) prescription patterns and their association with asthma-related outcomes globally. Herein, we examined SABA prescription and clinical outcomes in the Malaysian cohort of SABINA III.

Methods: In this observational, cross-sectional study, patients (≥12 years) were recruited between July and December 2019 from 15 primary and specialty care centres in Malaysia. Prescribed asthma treatments and severe exacerbation history within 12 months prior and asthma symptom control during the study visit were evaluated. Associations of SABA prescription with asthma control and severe exacerbation were analysed using multivariable regression models.

Results: Seven hundred thirty-one patients (primary care, n=265 [36.3%]; specialty care, n=466 [63.7%]) were evaluated. The prevalence of SABA over-prescription (≥3 SABA prescriptions/year) was 47.4% (primary care, 47.1%; specialty care, 47.6%), 51.8% and 44.5% among all patients and patients with mild and moderate-to-severe asthma, respectively. Altogether 9.0% (n=66) purchased SABA without a prescription; among them, 43.9% (n=29) purchased ≥3 inhalers. The mean (standard deviation) number of severe asthma exacerbations was 1.38 (2.76), and 19.7% (n=144) and 25.7% (n=188) had uncontrolled and partly controlled symptoms, respectively. Prescriptions of ≥3 SABA inhalers (vs 1–2) were associated with lower odds of at least partly controlled asthma (odds ratio=0.42; 95% confidence interval [CI]=0.27–0.67) and higher odds of having severe exacerbation(s) (odds ratio=2.04; 95% CI=1.44–2.89).

Conclusion: The prevalence of SABA over-prescription in Malaysia is high, regardless of the prescriber type, emphasising the need for healthcare providers and policymakers to adopt latest evidence-based recommendations to address this public health concern.

Introduction

Asthma is a chronic respiratory disease affecting up to 18% of the population across different countries.[1] In Malaysia, asthma is prevalent in approximately 4.5% of adults, among whom 68% experience exacerbation(s).[2] The mean cost of managing an acute exacerbation in the medical ward is Malaysian Ringgit 1777.86 per hospitalisation in a Malaysian suburban hospital,[3] representing a great financial burden for patients. Moreover, patients with mild asthma are at a high risk of experiencing acute asthma exacerbations, leading to a substantial disease burden in terms of hospitalisation, disease progression, impaired quality of life and mortality.[4–6]

Asthma requires optimal management with anti-inflammatory therapy, such as inhaled corticosteroids (ICSs) as first-line therapy, regardless of disease severity.[7] However, until 2019, the Global Initiative for Asthma (GINA) recommended the use of short-acting β_2-agonist (SABA) reliever monotherapy as step 1 treatment for patients with mild asthma.[8] Given the poor outcomes associated with SABA monotherapy, the GINA now recommends using low-dose ICS or as-needed ICS-

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formoterol therapy in adults and adolescents with mild asthma.[9,10] The use of as-needed ICS-formoterol therapy is based on evidence from several trials, including SYGMA 1, SYGMA 2, Novel START and PRACTICAL, which demonstrated the real-world efficacy of as-needed low-dose budesonide-formoterol in treating patients with mild asthma.[11–14]

In clinical practice, there is a reluctance to use ICSs and over-reliance on SABAs,[15] leading to poor ICS adherence and delay in ICS commencement for patients with mild asthma.[16,17] In a nationwide survey of prescription patterns, 98% and 76% of physicians in Malaysian public and private centres, respectively, selected inhaled SABAs as the preferred first-line therapy for patients with asthma.[18] Only 29% of physicians in both public and private centres chose ICSs as the preferred first-line therapy. In another study using data from the National Medical Care Survey in Malaysia, conducted in primary care centres, 50% and 23% of patients were prescribed inhaled SABAs and ICSs, respectively, whereas 33% were prescribed oral SABAs and oral corticosteroids.[19] Data on the prevalence and trends of inappropriate SABA use are needed to understand the public health burden of SABA over-reliance in asthma management.

The SABINA (SABA use IN Asthma) III study, part of the SABINA group of observational studies,[20] was designed to evaluate the status of SABA use and clinical outcomes in 24 countries worldwide. SABINA III (N=8351) revealed that 38.0% of patients with asthma had SABA over-prescriptions (≥3 inhalers/year).[21] Herein, we present data from a nationwide cohort of patients with asthma in Malaysia from the SABINA III study.

Methods

Study population

Patients aged ≥12 years with a documented diagnosis of asthma and ≥3 consultations with a physician at the time of enrolment were eligible for inclusion. All enrolled patients or their legal guardians provided written informed consent for study participation.

Study design

This multi-centre, observational, cross-sectional study was conducted at 15 primary and specialty care centres in Malaysia. Purposive sampling was used to select sites that were representative of current treatment practices in the country. Consecutive patients attending health clinics were enrolled from 29 July 2019 (first patient enrolled) to 15 December 2019 (last patient enrolled). Retrospective data were collected from existing patient medical records (both electronic and paper) along with patients' asthma symptoms by investigators during a designated clinic visit using a centrally designed electronic case report form.

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 on demographics, disease characteristics (severity according to 2017 GINA treatment recommendations),[22] medical history and comorbidities, prescribed asthma treatments and patient-reported over-the-counter (OTC) SABA purchase were collected.

SABA prescriptions issued by physicians were estimated using the average number of SABA inhaler/canister prescriptions per year. Collection of ≥3 SABA inhalers annually was considered over-prescription.[23] During the baseline period, patients were grouped by the number of collected SABA inhalers: 0, 1–2, 3–5, 6–9, 10–12 and ≥13.[24,25] ICS prescription included both monotherapy and fixed-dose combinations (ICS and long-acting β_2-agonist [LABA]), and the mean daily dose was defined as low, medium and high for each ICS.[26]

Study objectives and outcomes

The primary objectives of the study were a) to determine the pattern and trend of SABA prescription (inhalers/year) and identify the prevalence of SABA over-prescription and ICS prescription (by average daily dose) and b) to describe the demographic and clinical features of the population with asthma in Malaysia. The secondary objective was to describe the association between SABA prescription and clinical outcomes.

The outcomes included the level of asthma symptom control[22] (evaluated using the 2017 GINA assessment for asthma symptom control during the study visit) and the prevalence of severe asthma exacerbations[26] in the previous 12 months.

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Statistical analyses

All variables were analysed descriptively. For secondary analyses, logistic regression models were used to analyse the associations of SABA prescription with the level of asthma control (at least partly controlled asthma vs reference: uncontrolled asthma) and severe asthma exacerbation (severe asthma exacerbation 'yes' vs reference: severe asthma exacerbation 'no'). To ensure that the overall SABINA III study was adequately powered, we aimed to enrol up to 500 patients from each participating country, with 20–25 patients recruited from each participating site.[21]

All statistical tests were two-sided and conducted at a 5% level of significance using the R statistical software (version 3.6.0, The R Foundation for Statistical Computing, Vienna, Austria).

Appendix S1 provides additional methodological details.

Results

Study population

A total of 733 patients were enrolled, among whom 731 were analysed (Figure S1). Of them, 265 (36.3%) were managed by a primary care physician and 466 (63.7%) by a specialist (respiratory physician). Nearly two-thirds of the study population had moderate-to-severe asthma (n=478, 65.4%), and most of these patients were managed by a specialist (393/478, 82.2%). Most patients with mild asthma were managed in primary care centres (180/253, 71.1%).

The majority of the patients were women (79.6%), and the mean (standard deviation [SD]) age of the patients with asthma was 50.9 (15.0) years; most (91%) had fully reimbursed healthcare insurance (**Table 1** and **Appendix S2**).

Table 1. Patient demographics and clinical characteristics by practice type and asthma severity in the Malaysian cohort of SABINA III.

	Primary care (n=265)			Specialty care (n=466)			Total (N=732)*
	Mild asthma (n=180)	Moderate-to-severe asthma (n=85)	All (n=265)	Mild asthma (n=73)	Moderate-to-severe asthma (n=393)	All (n=466)	
Age, year, mean (SD)	49.77 (13.96)	54.74 (14.27)	51.36 (14.23)	49.33 (16.24)	50.96 (15.31)	50.71 (15.45)	50.93 (15.01)
Women, n (%)	144 (80.0)	64 (75.3)	208 (78.5)	55 (75.3)	319 (81.2)	374 (80.3)	583 (79.6)
Men, n (%)	36 (20.0)	21 (24.7)	57 (21.5)	18 (24.7)	74 (18.8)	92 (19.7)	149 (20.4)
BMI, kg/m^2, mean (SD)	28.19 (5.95)	29.63 (6.9)	28.65 (6.3)	28.58 (7.74)	28.74 (6.25)	28.72 (6.5)	28.69 (6.42)
25–29.9, n (%)	61 (33.9)	25 (29.4)	86 (32.5)	26 (35.6)	127 (32.3)	153 (32.8)	240 (32.8)
≥30, n (%)	62 (34.4)	37 (43.5)	99 (37.4)	24 (32.9)	151 (38.4)	175 (37.6)	274 (37.4)
Smoking status							
Active smoker	6 (3.3)	0 (0.0)	6 (2.3)	2 (2.7)	4 (1.0)	6 (1.3)	12 (1.6)
Former smoker	11 (6.1)	8 (9.4)	19 (7.2)	5 (6.8)	25 (6.4)	30 (6.4)	49 (6.7)
Never smoker	163 (90.6)	77 (90.6)	240 (90.6)	66 (90.4)	364 (92.6)	430 (92.3)	671 (91.7)
Educational level							
Primary school	25 (13.9)	14 (16.5)	39 (14.7)	3 (4.1)	51 (13.0)	54 (11.6)	93 (12.7)
Secondary school	103 (57.2)	50 (58.8)	153 (57.7)	39 (53.4)	159 (40.5)	198 (42.5)	352 (48.1)
High school	22 (12.2)	10 (11.8)	32 (12.1)	9 (12.3)	34 (8.7)	43 (9.2)	75 (10.2)
University or higher	26 (14.4)	11 (12.9)	37 (14.0)	20 (27.4)	132 (33.6)	152 (32.6)	189 (25.8)
Unknown	4 (2.2)	0 (0.0)	4 (1.5)	2 (2.7)	17 (4.3)	19 (4.1)	23 (3.1)
Healthcare insurance or medical funding							
Not reimbursed	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.1)	35 (8.9)	38 (8.2)	38 (5.2)
Partially reimbursed	0 (0.0)	0 (0.0)	0 (0.0)	7 (9.6)	19 (4.8)	26 (5.6)	26 (3.6)
Fully reimbursed	180 (100.0)	85 (100.0)	265 (100.0)	60 (82.2)	339 (86.3)	399 (85.6)	665 (90.8)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.1)	0 (0.0)	3 (0.6)	3 (0.4)
Comorbidities							
None	43 (23.9)	10 (11.8)	53 (20.0)	25 (34.2)	98 (24.9)	123 (26.4)	177 (24.2)
1–2	100 (55.6)	36 (42.4)	136 (51.3)	37 (50.7)	192 (48.9)	229 (49.1)	365 (49.9)
3–4	36 (20.0)	30 (35.3)	66 (24.9)	11 (15.1)	82 (20.9)	93 (20.0)	159 (21.7)
≥5	1 (0.6)	9 (10.6)	10 (3.8)	0 (0.0)	21 (5.3)	21 (4.5)	31 (4.2)

BMI, body mass index; SABA, short-acting β_2-agonist; SABINA, SABA use IN Asthma; SD, standard deviation.
*Data were missing for one patient.

SABA over-prescription and purchase

Overall, SABA over-prescription was observed in 47.4% of patients; among those with mild and moderate-to-severe asthma, the prevalence was 51.8% and 44.5%, respectively (Figure 1A and B). The prevalence of SABA over-prescription was higher in patients with mild asthma than in those with moderate-to-severe asthma (53.3% vs 33.7%) in primary care setting but was comparable in specialty care setting (48.0% vs 47.6%). The prevalence of SABA over-prescription without ICSs was substantially higher in primary care setting than in specialty care setting (22.5% vs 6.6%; **Appendix S2** and **Figure S2**). Conversely, the prevalence of SABA over-prescription with ICSs was higher in specialty care setting than in primary care setting (46.7% vs 28.8%). Purchase of SABA without a prescription was reported by 9.0% (n=66) of all patients; among them, 43.9% (n=29) purchased ≥3 inhalers.

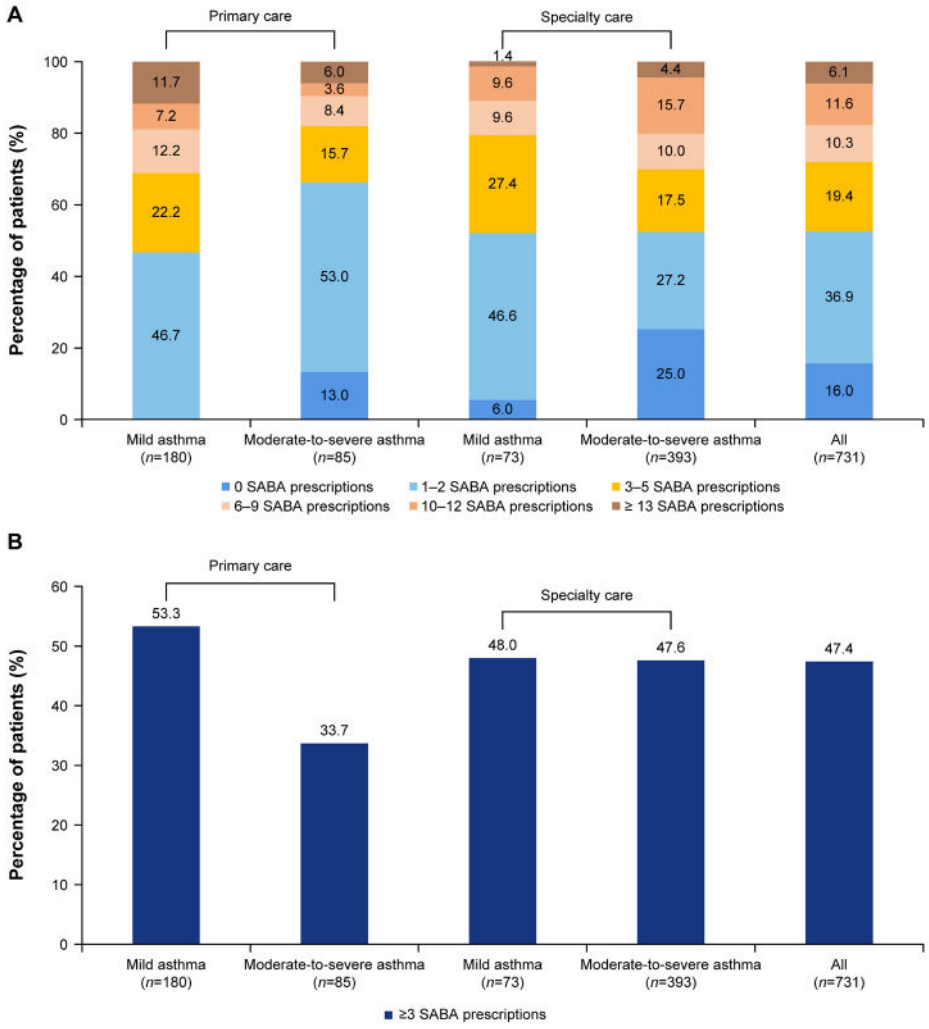

Figure 1. SABA prescription in patients with asthma among the Malaysian cohort of SABINA III. (A) SABA prescription and (B) SABA over-prescription in patients with mild and moderate-to-severe asthma managed in primary and specialty care settings. SABA over-prescription was defined as prescription of ≥3 SABA canisters/inhalers in the previous 12 months. SABA, short-acting β_2-agonist; SABINA, SABA use IN Asthma

Asthma disease characteristics and treatment

The mean (SD) duration of asthma was 23.6 (16.7) years (Table 2). The mean (SD) number of severe asthma exacerbations in the previous 12 months was 1.38 (2.76) and was higher in primary care setting than in specialty care setting for both mild (1.27 [2.51] vs 0.92 [1.93]) and moderate-to-severe (1.6 [2.32] vs 1.47 [3.06]) asthma. Half of the study population (n=366, 50%) experienced at least one severe exacerbation, while 17% (n=125) experienced ≥3 severe exacerbations in the previous 12 months.

Table 2. Asthma disease characteristics and treatment by practice type and asthma severity in the Malaysian cohort of SABINA III.

Disease characteristics	Primary care (n=265)		Specialty care (n=466)		Total (N=732)*
	Mild asthma (n=180)	Moderate-to-severe asthma (n=85)	Mild asthma (n=73)	Moderate-to-severe asthma (n=393)	
Asthma duration, year, mean (SD)	23.74 (16.88)	25.67 (16.25)	21.95 (17.01)	23.41 (16.67)	23.59 (16.69)
GINA treatment step					
Step 1	37 (20.6)	0	7 (9.6)	0	44 (6.0)
Step 2	143 (79.4)	0	66 (90.4)	0	209 (28.6)
Step 3	0	33 (38.8)	0	111 (28.2)	144 (19.7)
Step 4	0	46 (54.1)	0	243 (61.8)	289 (39.5)
Step 5	0	6 (7.1)	0	39 (9.9)	45 (6.1)
Number of severe exacerbations in the previous 12 months, mean (SD)	1.27 (2.51)	1.6 (2.32)	0.92 (1.93)	1.47 (3.06)	1.38 (2.76)
No. of patients with severe exacerbations in the previous 12 months, *n* (%)	28.19 (5.95)	29.63 (6.9)	28.58 (7.74)	28.74 (6.25)	28.69 (6.42)
0	87 (48.3)	38 (44.7)	48 (65.8)	192 (48.9)	366 (50.0)
1	43 (23.9)	19 (22.4)	8 (11.0)	91 (23.2)	161 (22.0)
2	17 (9.4)	9 (10.6)	8 (11.0)	46 (11.7)	80 (10.9)
3	21 (11.7)	6 (7.1)	5 (6.8)	21 (5.3)	53 (7.2)
>3	12 (6.7)	13 (15.3)	4 (5.5)	43 (10.9)	72 (9.8)
Asthma symptom control					
Well controlled	93 (51.7)	50 (58.8)	46 (63.0)	210 (53.4)	400 (54.6)
Partly controlled	52 (28.9)	22 (25.9)	20 (27.4)	94 (23.9)	188(25.7)
Uncontrolled	35 (19.4)	13 (15.3)	7 (9.6)	89 (22.6)	144 (19.7)
Treatment					
SABA alone, n (%)	32 (17.8)	0 (0)	5 (6.8)	1 (0.3)	38 (5.2)
Total use in the previous 12 months (canisters/inhalers), mean (SD)	6.2 (5.9)	-	5.4 (6.0)	3.0 (NA)	6.0 (5.8)
SABA as add-on to maintenance therapy, n (%)	148 (82.2)	74 (87.1)	64 (87.7)	294 (74.8)	580 (79.2)
Total use in the previous 12 months (canisters/inhalers), mean (SD)	4.7 (4.7)	3.6 (4.1)	3.7 (3.3)	6.0 (5.4)	5.1 (5.0)
Duration of use, day	55.3 (47.2)	29.0 (NA)	48.0 (15.6)	60.9 (40.9)	58.5 (40.1)
ICS, n (%)	148 (82.2)	24 (28.2)	61 (83.6)	39 (9.9)	272 (37.2)
Total use in the previous 12 months (canisters/inhalers), mean (SD)	4.5 (3.6)	3.0 (2.9)	5.4 (4.9)	4.5 (4.5)	4.6 (4.0)
Total daily dose, n (%)					
Low dose	48 (32.7)	2 (9.5)	33 (54.1)	6 (17.1)	89 (33.7)
Medium dose	86 (58.5)	17 (81)	27 (44.3)	28 (80)	158 (59.8)
High dose	13 (8.8)	2 (9.5)	1 (1.6)	1 (2.9)	17 (6.4)
Duration of use, day, mean (SD)	725.1 (908.1)	2621.1 (4748.2)	322.5 (435.6)	680.9 (1071.6)	903.6 (2026.9)
ICS/LABA (fixed-dose combination), n (%)	0 (0)	71 (83.5)	14 (19.2)	384 (97.7)	470 (64.2)
Total use in the previous 12 months (canisters/inhalers), mean (SD)	NA	59.5 (63.4)	28.2 (56.3)	42.9 (62.7)	44.9 (62.8)
Total daily dose, n (%)					
Low dose	NA	10 (14.3)	7 (53.8)	68 (17.8)	85 (18.2)
Medium dose	NA	54 (77.1)	6 (46.2)	270 (70.5)	331 (70.9)
High dose	NA	6 (8.6)	0 (0)	45 (11.7)	51 (10.9)
Duration of use, day	NA	90.0 (NA)	50.7 (30.9)	52.3 (29.4)	53.2 (29.5)
OCS burst treatment/short course, n (%)	43 (23.9)	30 (35.3)	17 (23.3)	149 (37.9)	239 (32.7)

Table 2. Continued

Disease characteristics	Primary care (n=265)		Specialty care (n=466)		Total (N=732)*
	Mild asthma (n=180)	Moderate-to-severe asthma (n=85)	Mild asthma (n=73)	Moderate-to-severe asthma (n=393)	
Total daily dose (mg/day), mean (SD)	30.0 (4.4)	30.0 (0.0)	29.1 (3.8)	39.3 (47.9)	35.7 (38.2)
Number of days per prescription, mean (SD)	5.0 (0.7)	5.0 (1.1)	4.4 (1.2)	4.4 (1.4)	4.6 (1.3)
OCS long-term/maintenance dosing, n (%)	5 (2.8)	1 (1.2)	0 (0)	24 (6.1)	30 (4.1)
Total use in the previous 12 months (canisters/inhalers), mean (SD)	0.0 (0.0)	0.0 (0.0)	–	13.5 (62.5)	10.7 (55.7)
Total daily dose (mg/day), mean (SD)	20.0 (44.7)	200.0 (NA)	–	48.2 (85.4)	48.6 (83.6)
Duration of use, day	NA (NA)	NA (NA)	–	15.0 (21.2)	15.0 (21.2)
Antibiotics (prescribed for asthma only), n (%)	3 (1.7)	7 (8.4)	7 (9.6)	65 (16.5)	82 (11.3)
Total daily dose (mg/day), mean (SD)	1658.3 (194.2)	1178.6 (301.2)	1453.6 (406.3)	1550.4 (2230.8)	1514.3 (1990.9)
Duration of use, day	0.0 (0.0)	0.0 (0.0)	5.2 (12.7)	2.0 (7.7)	2.0 (7.6)

ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; NA, not available; OCS, oral corticosteroid; SABA, short-acting β_2-agonist; SABINA, SABA use IN Asthma; SD, standard deviation.
*Data were missing for one patient.

Overall, 19.7% (n=144) and 25.7% (n=188) of the patients had uncontrolled and partly controlled symptoms, respectively (**Table 2**). The proportion of patients with moderate-to-severe asthma who had uncontrolled disease was higher than that of those with mild asthma (21.3% vs 16.6%).

SABA alone was prescribed in 5.2% (n=38) of the patients (**Table 2**). Most patients were prescribed SABA along with maintenance therapy (n=580, 79.2%). ICSs were prescribed in 37.2% (n=272), and those with mild asthma accounted for >80% of this subgroup. For mild asthma, low-dose ICSs were more commonly prescribed in specialty care setting than in primary care setting (54.1% vs 32.7%); meanwhile, high-dose ICSs were more commonly prescribed in primary care setting than in specialty care setting (8.8% vs 1.6%).

A fixed-dose combination of ICS/LABA was prescribed in 64.2% (n=470), mostly among those with moderate-to-severe asthma. A total of 239 (32.7%) patients received oral corticosteroid burst prescriptions, and the prevalence was comparable between primary and specialty care settings. Appendix S2 provides additional details.

SABA prescriptions and clinical outcomes

More patients had uncontrolled asthma in the ≥3 SABA group than in the 1–2 SABA group (24.7% vs 12.9%; **Table 3**), and patients prescribed ≥3 SABA inhalers had greater odds of having uncontrolled asthma than those prescribed 1–2 SABA inhalers (adjusted odds ratio [OR]=0.42; 95% confidence interval [CI]=0.27–0.67; **Figure 2A**).

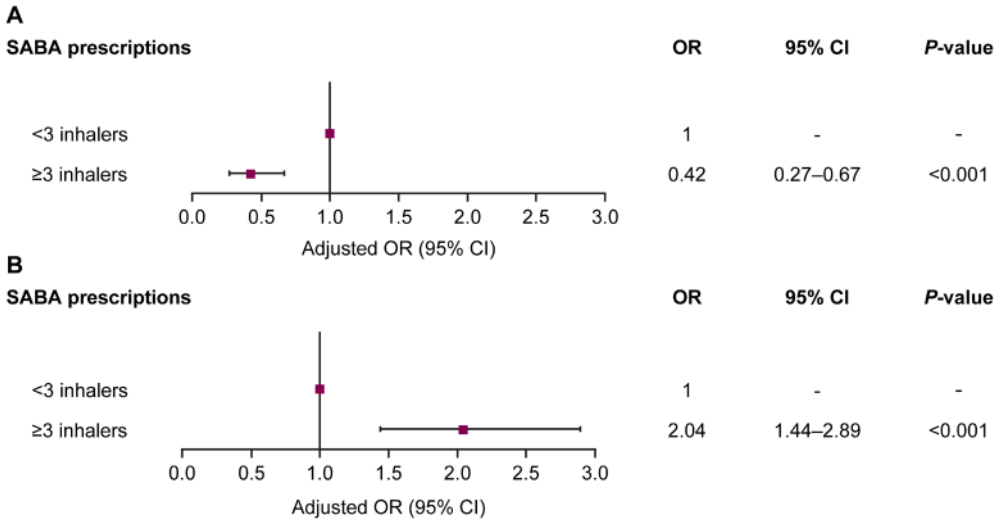

Figure 2. Association of SABA prescriptions with the level of asthma symptom control and severe exacerbations in the previous 12 months among the Malaysian cohort of SABINA III. (A) Adjusted OR of achieving at least partly controlled asthma according to SABA inhaler prescriptions in the previous 12 months (reference: uncontrolled asthma) (n=588). (B) Adjusted OR of experiencing a severe asthma exacerbation by SABA inhaler prescriptions in the previous 12 months (n=588). Based on the covariable significance in the models, the ORs were corrected for age, sex, BMI, asthma duration, smoking history, comorbidity, GINA step, practice type, healthcare insurance reimbursement and educational level. At least partly controlled asthma was defined as partly controlled plus well-controlled asthma. BMI, body mass index; CI, confidence interval; GINA, Global Initiative for Asthma; OR, odds ratio; SABA, short-acting β_2-agonist; SABINA, SABA use IN Asthma.

Similarly, patients prescribed ≥3 SABA inhalers/year had more severe exacerbations than those prescribed 1–2 SABA inhalers/year (60.5% vs 43.6%; **Table 3**).

Patients over-prescribed SABA were also two times more likely to experience severe exacerbations in the previous 12 months (adjusted OR=2.04; 95% CI=1.44–2.87; Figure 2B).

Table 3. Level of asthma symptom control and severe exacerbation across SABA inhaler prescription categories in the Malaysian cohort of SABINA III.

	SABA prescriptions in the previous 12 months		
	1–2 inhalers	≥3 inhalers	Total
Level of asthma symptom control, n (%)			
Patients with uncontrolled asthma	24 (12.9)	80 (24.7)	114 (19.4)
Patients with at least partly controlled asthma*	230 (87.1)	244 (75.3)	474 (80.6)
Total	264	324	588
Patients with at least one severe exacerbation in the previous 12 months, n (%)			
≥1 exacerbation	115 (43.6)	196 (60.5)	311 (52.9)
0 exacerbations	149 (56.4)	128 (39.5)	277 (4.1)
Total	264	324	58

SABA, short-acting β_2-agonist; SABINA, SABA use IN Asthma.
*At least partly controlled asthma was defined as partly controlled plus well-controlled asthma.

Discussion

In this real-world, nationwide cohort study in Malaysia based on data from SABINA III, nearly half of the patients with asthma were over-prescribed SABA, and the prevalence of SABA over-prescription was similar irrespective of where the patients were treated (primary or specialty care). Asthma morbidity was high among the study population, with about 50% of patients experiencing ≥1 severe exacerbation in the previous 12 months and 45% having partly controlled or uncontrolled asthma.

The prevalence of SABA over-prescription among the Malaysian cohort (47.4%) is substantially higher than that among European cohorts (9%–38%),[27–29] the overall SABINA III cohort (38.0%) and the SABINA III Asian cohort (26.7%).[30] Moreover, 6.1% of patients among the Malaysian cohort were prescribed >12 SABA prescriptions. This finding is concerning, as SABA overuse is associated with poor asthma-related outcomes[28,29,31]; in particular, the use of ≥12 SABA inhalers/year is associated with an increased risk of mortality.[32] The high prevalence of SABA over-prescription in this cohort may be explained by disease severity being assessed in accordance with GINA 2017 recommendations, which were in place at the time of study implementation and advocated use of as-needed SABA alone for GINA step 1-treated patients.[22] Overall, 9% of the study population purchased SABA directly from pharmacists OTC without a prescription, of whom 44% purchased ≥3 inhalers. Some patients may not have reported OTC SABA purchase, or there may have been loss of follow-up with their physician.[33] In Malaysia, SABA inhalers or tablets can be purchased from community pharmacists without a prescription, which accounts for a large proportion of the total number of SABAs dispensed annually (47%).[34] Therefore, the number of OTC SABA purchases could be greater than that reported in this study, and there is a high likelihood of patients overusing their SABAs owing to such an unregulated source of the medication. Addressing this concern through patient education and policy measures is critical to prevent SABA overuse among patients with asthma.

A key finding of the present study was the high prevalence of severe asthma exacerbations in the previous 12 months. The Asia Pacific Asthma Insight and Management Survey showed that approximately 32% of patients with asthma surveyed in Malaysia experienced an exacerbation annually.[35] Similarly, the 2014 National Medical Care Survey in Malaysia reported an exacerbation prevalence of 24.4% in patients with asthma in primary care setting.[19] Although previous studies conducted in Malaysia have not evaluated comorbidities, the high exacerbation burden observed in this Malaysian cohort may be attributable to the substantial proportion of patients who reported ≥1 comorbidity (75.8%). Indeed, previous reports have documented associations between comorbidities and the frequency of annual hospitalisations owing to asthma exacerbation[36] and SABA over-prescription.[37] Moreover, SABA over-prescription was associated with increased odds of experiencing a severe exacerbation. This is consistent with findings from other SABINA studies globally, including the SABINA III study,[21] wherein the use of ≥3 SABA inhalers in a year was associated with an increased risk of severe asthma exacerbation.[28,29] Another possible explanation for the high exacerbation rate observed in this study is the substantial disease burden in patients with mild asthma; indeed, 46.6% of the patients with mild asthma experienced ≥1 severe exacerbation in the previous 12 months. Notably, the exacerbation burden was particularly high in patients with milder disease treated in primary care setting. A higher proportion of patients with mild asthma were prescribed ≥3 SABA inhalers in primary care setting than in specialty care setting (53.3% vs 48.0%), which is suggestive of an underestimation of the underlying disease severity and inappropriate management, resulting in suboptimal symptom control.[38] Indeed, a substantially higher proportion of patients with mild asthma in primary care setting than in specialty care setting reported partly controlled/uncontrolled asthma (48.3% vs 37.0%) and experienced ≥1 severe asthma exacerbation (51.7% vs 34.2%). These findings may be attributable to the overestimation of asthma control by both patients[39] and primary care physicians,[40] resulting in undertreatment of the disease[41] and increased reliance on SABAs for symptom relief.[42] Taken together, these findings underscore the need for regular monitoring of SABA prescriptions and symptom control and implementing comprehensive management plans involving a multidisciplinary approach.

The proportion of patients with good symptom control assessed using the GINA classification is slightly higher in our study than in the ASCOPE study, which enrolled patients with asthma across primary care centres in Malaysia: 41% of patients had well controlled asthma in the ASCOPE study compared with 54.6% in our study.[43] The high rate of well-controlled symptoms in the Malaysia cohort could be attributed to the inclusion of a large number of patients managed in specialty care setting (63.7%). Nevertheless, SABA over-prescription was associated with poorer asthma symptom control, suggesting the need for treatment optimisation with ICS/LABA (e.g. budesonide-formoterol maintenance and reliever therapy), as evidenced by the high level of asthma control and satisfaction among Malaysian patients with asthma in the SMARTEST study.[44]

Our findings contribute to accumulating evidence that SABA overuse is widespread, indicating that it is a public health issue that needs to be addressed. The recent GINA report does not propose the use of SABA therapy alone in patients with asthma and instead recommends ICS-formoterol as needed in patients with asthma of all severities.[10] Herein, ICS therapy was prescribed to most patients with mild asthma (82.2% in primary care setting and 83.6% in specialty care setting); however, no patients with mild asthma managed in primary care setting and only 19% of patients managed in specialty care setting received ICS/LABA combination therapy. While it is unclear whether ICS/LABA was used as an as-needed reliever, our results indicated that SABA as an add-on to maintenance therapy was still prescribed to patients with mild asthma in both primary (82.2%) and specialty (87.7%) care setting. ICS/LABA therapy was prescribed to most patients with moderate-to-severe asthma; however, the prevalence of SABA prescription was still high, especially in primary care setting. Taken together, there is a high unmet need for changing local clinical practices and physician and patient behaviours towards SABA use for asthma. Our findings have the potential to drive changes in prescription habits, whereby low-dose ICS-formoterol is the preferred reliever medication (Track 1 of GINA 2022).[10] For patients prescribed SABA as a reliever (alternative approach in Track 2 of GINA 2022), concomitant ICSs should be prescribed.[10] Prescribers should also ensure a clear limit of usage as written in the prescription and strictly enforce a one-to-one exchange of SABA medication when patients request replenishment of their medication. In addition, the Malaysian asthma clinical practice guidelines should be adapted in line with current GINA recommendations[10] to eliminate the use of SABA monotherapy and promote the appropriate use of ICS-based therapies. National healthcare policies should be updated in agreement with global quality standards on improving asthma outcomes[45] to prevent unnecessary SABA exposure among patients with asthma.

To our knowledge, this study is the first to compare asthma prescription patterns between primary and specialty care settings in Malaysia, with a patient population large enough to identify gaps in such patterns. However, patient recruitment was skewed towards specialty care; therefore, the study population may not fully represent national prescription patterns. Additionally, the study collected data on SABA prescriptions that may not fully reflect actual SABA use. Inhaler technique was also not assessed, which is a potential variable that affects asthma control. In addition, the comparisons of the outcomes between primary and specialty care settings were descriptive in nature, with no formal statistical analyses performed. The high prevalence of SABA over-prescription in the present cohort may be explained by the assessment of disease severity based on GINA 2017 recommendations (in place at the time of study conception and implementation). Finally, our study precluded the determination of the cause–effect relationship between SABA prescriptions and severe asthma exacerbations. Therefore, our findings demonstrate an association, and not causality, between SABA over-prescription and severe asthma exacerbation. Nevertheless, our results could be an important starting point for policymakers to establish that SABA over-prescription is associated with asthma morbidity.

Conclusion

This nationwide SABINA study demonstrated that SABA over-prescription is highly prevalent among patients with asthma in Malaysia, potentially putting them at a high risk of severe exacerbations and asthma-

related mortality. These findings emphasise the need for monitoring SABA prescriptions and usage, updating national treatment guidelines and improving the implementation of evidence-based therapies in patients with asthma.

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Author contributions

Andrea Yu-Lin Ban contributed to data collection, data analysis, data interpretation, and drafting and reviewing of the manuscript.
Paranthaman Vengadasalam contributed to data collection, data analysis, data interpretation, and drafting and reviewing of the manuscript.
Sri Wahyu Taher contributed to data collection, data analysis, data interpretation, and drafting and reviewing of the manuscript.
Mohd Arif Mohd Zim contributed to data collection, data analysis, data interpretation, and drafting and reviewing of the manuscript.
Syazatul Syakirin Sirol Aflah contributed to data collection, data analysis, data interpretation, and drafting and reviewing of the manuscript.
Ummi Nadira Daut contributed to data collection, data analysis, data interpretation, and drafting and reviewing of the manuscript.
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Lalitha Pereirasamy contributed to data collection, data analysis, data interpretation, and drafting and reviewing of the manuscript.
Azza Omar contributed to data collection, data analysis, data interpretation, and drafting and reviewing of the manuscript.
Aishah Ibrahim contributed to data collection, data analysis, data interpretation, and drafting and reviewing of the manuscript.
Noor Aliza Mohd Tarekh contributed to data collection, data analysis, data interpretation, and drafting and reviewing of the manuscript.
Swee Kim Chan contributed to data collection, data analysis, data interpretation, and drafting and reviewing of the manuscript.
Norsiah Ali contributed to data collection, data analysis, data interpretation, and drafting and reviewing of the manuscript.
Nor Azila Mohd Isa contributed to data collection, data analysis, data interpretation, and drafting and reviewing of the manuscript.
Husni Hussain contributed to data collection, data analysis, data interpretation, and drafting and reviewing of the manuscript.
Noraziah Abdul Karim contributed to data collection, data analysis, data interpretation, and drafting and reviewing of the manuscript.
Vieshal Raja Gopal contributed to data collection, data analysis, data interpretation, and drafting and reviewing of the manuscript.
Sue Yin Chiam contributed to data collection, data analysis, data interpretation, and drafting and reviewing of the manuscript.
Maarten J.H.I. Beekman designed the study and contributed to data collection, data analysis, data interpretation, and drafting and reviewing of the manuscript.

Ethical approval

All enrolled patients or their legal guardians provided written informed consent for participation in the study. 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. Ethical approval for this study was obtained from the Medical Research and Ethics Committee, Ministry of Health, Malaysia.

Conflicts of interest

Andrea Yu-Lin Ban received honoraria from AstraZeneca, Boehringer Ingelheim, Novartis and Bayer Co. as well as travel support and sample drugs from AstraZeneca and served as an advisory board member of the 'Use of ICS/LABA in Covid-19' for AstraZeneca and a committee member of the Malaysian Thoracic Society. **Paranthaman Vengdasalam** received honoraria from AstraZeneca and Mundipharma Pharmaceuticals as well as travel support and sample drugs from AstraZeneca and GlaxoSmithKline Pharmaceutical and served as a member of the MFP Editorial Board, Perak Medical Journal Editorial Board, Academy of Family Physician Malaysia and GCFM Post graduate board. **Sri Wahyu Taher**

received honoraria from AstraZeneca, GlaxoSmithKline Pharmaceutical and Novo Nordisk Pharma as well as travel support from AstraZeneca, Novo Nordisk Pharma and Sanofi-Aventis and sample drugs from AstraZeneca and served as an advisory board member of Novo Nordisk Pharma and president of the Family Medicine Specialist Association Malaysia. **Mohd Arif Mohd Zim** received honoraria from AstraZeneca, Orient EuroPharma, Novartis and GlaxoSmithKline Pharmaceutical as well as travel support and sample drugs from AstraZeneca and served on the Severe Asthma Advisory Board for AstraZeneca and as a member of PRECISION (Severe Asthma Working Group) for AstraZeneca and the Malaysian Association of Bronchology and Interventional Pulmonology. **Syazatul Syakirin Sirol Aflah** received honoraria from AstraZeneca, GlaxoSmithKline Pharmaceutical, Orient EuroPharma and Mundipharma Pharmaceuticals as well as travel support from AstraZeneca and Mundipharma Pharmaceuticals and served as a committee member of the Malaysian Thoracic Society. **Ummi Nadira Daut** received honoraria from AstraZeneca, Orient EuroPharma, Novartis Corporation and GlaxoSmithKline Pharmaceutical and travel support from AstraZeneca. **Irfhan Ali Hyder Ali** received honoraria from AstraZeneca, Boehringer Ingelheim, Orient EuroPharma, Novartis, GlaxoSmithKline Pharmaceutical and Pfizer as well as travel support from AstraZeneca, Boehringer Ingelheim, Orient EuroPharma, Novartis and Pfizer and sample drugs from AstraZeneca, Novartis and Boehringer Ingelheim and served as a committee member of the Malaysian Thoracic Society, head of the Respiratory Services, Malaysia and head of the Respiratory Department, Penang Hospital. **Lalitha Pereirasamy** received honoraria from AstraZeneca, Novartis and GlaxoSmithKline Pharmaceutical as well as travel support and sample drugs from AstraZeneca and served as a committee member of the Malaysian Thoracic Society. **Azza Omar** received honoraria from AstraZeneca, GlaxoSmithKline Pharmaceutical, Boehringer Ingelheim, Novartis, Orient EuroPharma, Sanofi-Aventis and Mundipharma Pharmaceuticals as well as travel support and sample drugs from AstraZeneca and served as a committee member and 'Severe Asthma Diagnostic Consensus' lead of the Malaysian Thoracic Society and a member of PRECISION (Severe Asthma Working Group) for AstraZeneca. **Aishah Ibrahim** received honoraria from AstraZeneca, Boehringer Ingelheim, Novartis, Orient EuroPharma and GlaxoSmithKline Pharmaceutical as well as travel support and sample drugs from AstraZeneca and served as a committee member of the Malaysian Thoracic Society. **Noor Aliza Mohd Tarekh** received honoraria, travel support and sample drugs from AstraZeneca. **Norsiah Ali** received honoraria, travel support and sample drugs from AstraZeneca and served as a past-president of the Family Medicine Specialist Association, Malaysia. **Nor Azila Mohd Isa** received honoraria, travel support and sample drugs from AstraZeneca and served as a member of the Family Medicine Specialist Association, Malaysian Thoracic Society and Islamic Medical Association, Malaysia. **Husni Hussain** received honoraria and travel support from AstraZeneca and served as a committee member of the Family Medicine Specialist Selangor Association. **Vieshal Raja Gopal** and **Sue Yin Chiam** are employees of AstraZeneca. **Maarten J.H.I. Beekman** was an employee of AstraZeneca at the time the study was conducted and holds stocks of AstraZeneca. **Swee Kim Chan** and **Noraziah Abdul Karim** have nothing to disclose.

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Data sharing statement

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. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

How does this paper make a difference in general practice?

- In the Malaysian cohort of SABINA III, we observed that prescription of ≥3 SABA inhalers/year is widespread, occurring in almost half of the study patients.
- SABA over-prescription was associated with poorly controlled asthma and increased prevalence of severe exacerbations, indicating the need for improvements in asthma management across the country.

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Appendix S1-METHODS

Study population

Patients were excluded if they had a diagnosis of chronic obstructive pulmonary disease, 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 enrolled patients were representative of the real-world population in Malaysia.

Study design

No additional mandated interventions on top of routinely performed physician visits, examinations or treatments were required, other than the 2017 GINA assessment of asthma symptom 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 during one visit.

Data variables

To enable the comparison of different types and number of doses of SABA canisters, a standardised threshold for appropriate SABA use was defined as 150 doses/puffs/actuations per year, approximating ≤2 canisters per year (based on the British Thoracic Society guidelines and GINA recommendations of 3 SABA puffs/week). In the present study, SABA over prescription was defined assuming that 2 puffs were used on each occasion and that a patient with well-controlled asthma would not use their SABA reliever more than twice/week, which equals a maximum of 2 SABA canisters per year.[1]

Based on the number of SABA and ICS prescriptions over the preceding 12 months, patients with mild asthma were grouped into 5 categories: a) no prescriptions for asthma inhalers, b) ≤2 SABA prescriptions with no ICS, c) ≤2 SABA prescriptions with ICS, d) ≥3 SABA prescriptions with no ICS and e) ≥3 SABA prescriptions with ICS. Similarly, patients with moderate-to-severe asthma were grouped into 2 categories: a) ≤2 SABA prescriptions on top of maintenance therapy and b) ≥3 SABA prescriptions on top of maintenance therapy.

Statistical analysis

Covariates for the secondary analysis included age (continuous), gender, body mass index (BMI) (continuous), education, healthcare insurance (not reimbursed, partially reimbursed or fully reimbursed), practice type (primary or specialty care), investigator-classified asthma severity (guided by GINA 2017 treatment steps: steps 1–2, mild asthma; steps 3–5, moderate-to-severe asthma), asthma duration (continuous), number of comorbidities (0, 1–2, 3–4 or ≥5) and smoking status (active, former or never smoker).

References

1. Bateman ED, Hurd SS, Barnes PJ, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J*. 2008;31(1):143–178.

Appendix S2- RESULTS

Study population

The mean (SD) BMI of the study population was 28.7 (6.4) kg/m^2, and 70.2% of patients were overweight or obese (BMI ≥25 kg/m^2). Approximately half of the study population had 1 or 2 comorbidities (49.9%; **Table 1**).

Patterns of SABA and ICS prescriptions

In an analysis of SABA and ICS prescriptions in patients with mild asthma (Figure S2A), ≤2 canisters of SABA with ICS were prescribed for 31.2% of patients treated in primary care and 36.7% of patients treated in specialty care. In addition, ≤2 canisters of SABA without ICS were prescribed for 17.5% and 10% of patients treated in primary and specialty care, respectively. SABA over prescription (≥3 canisters) without ICS was substantially higher in patients treated at primary vs specialty care (22.5% vs 6.6%). Conversely, SABA over prescription with ICS was higher in specialty vs primary care (46.7% vs 28.8%).

Among patients with moderate-to-severe asthma, the prevalence of SABA over-prescription on a background of maintenance therapy was 47.4% in patients treated in specialty care vs 33.8% in those treated in primary care (**Figure S2B**).

Asthma disease characteristics and treatment

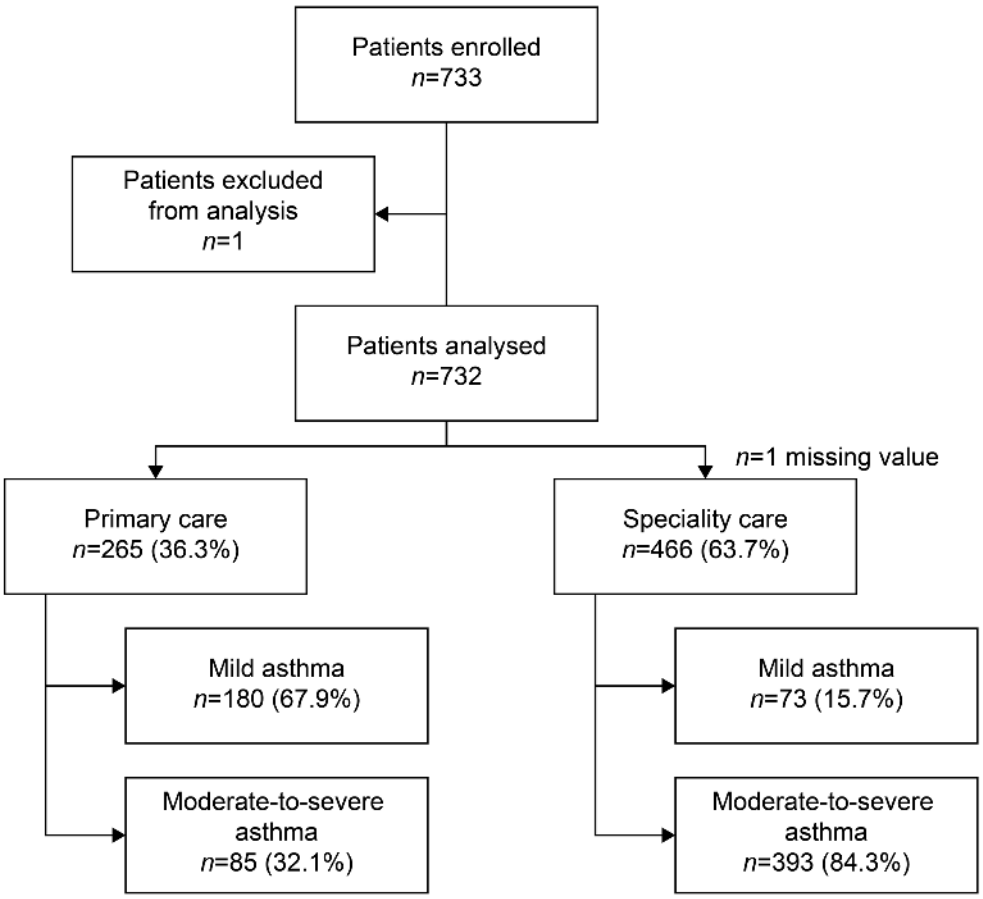
Among patients with mild asthma, the incidence of severe exacerbations in the previous 12 months was generally higher for those managed at primary vs specialty care (1 exacerbation: 23.9% vs 11.0%; 2 exacerbations: 9.4% vs 11.0%; 3 exacerbations: 11.7% vs 6.8%; >3 exacerbations: 6.7% vs 5.5%). Among patients with moderate-to-severe asthma, the incidence of severe exacerbations was mostly comparable between those treated in primary and specialty care. However, the incidence of 3 (7.1% vs 5.3%) or >3 (15.3% vs 10.9%) exacerbations was higher in those treated in primary vs specialty care (**Table 2**).

Among patients with mild asthma, the prevalence of uncontrolled symptoms was higher in those treated in primary vs specialty care (19.4% vs 9.6%); conversely, among patients with moderate-to-severe asthma, this prevalence was higher in those treated in specialty care (22.6% vs 15.3%; **Table 2**).

Overall, a fixed-dose combination of ICS/LABA was prescribed in 64.2% (n=470), mostly in patients with moderate-to-severe asthma. No patients with mild asthma treated in primary care received ICS/LABA combination therapy, whereas it was prescribed in a minority of patients with mild asthma treated at specialty care (14/73, 19.2%).

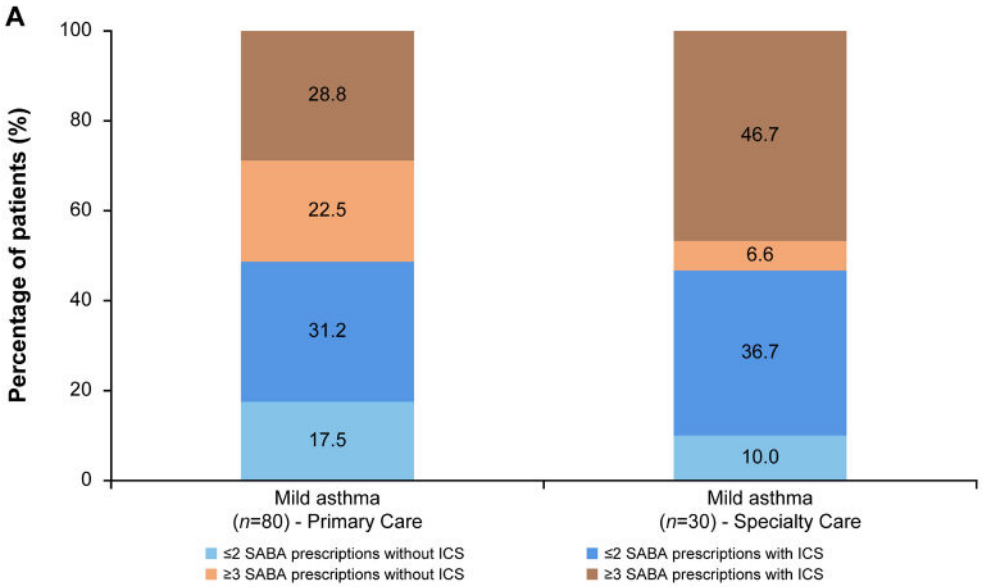
Long-term or maintenance treatment with OCS or antibiotics was prescribed in 30 (4.1%) and 82 (11.3%) patients, respectively, mostly in patients with moderate-to-severe asthma treated in specialty care.

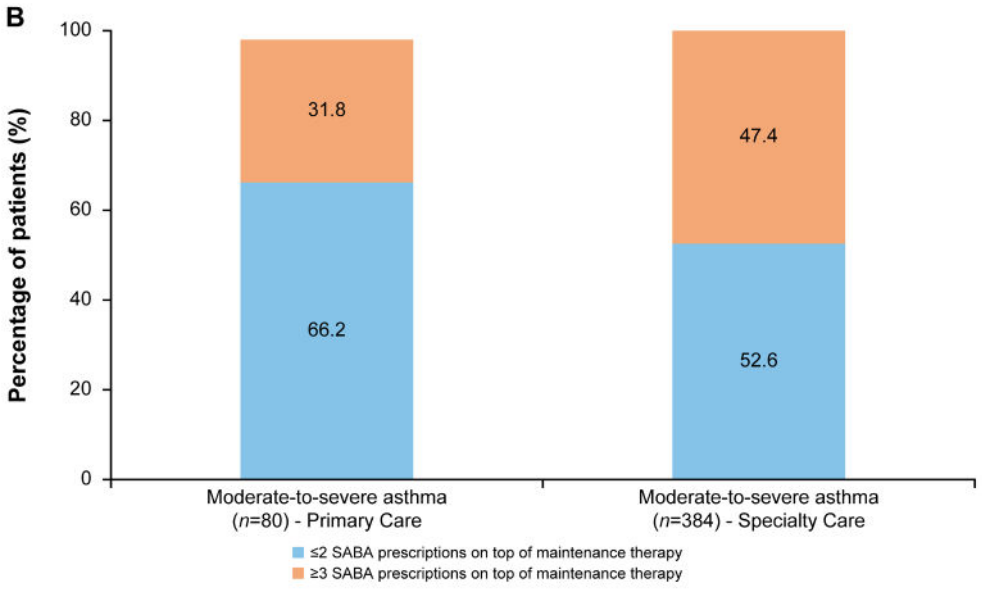
Figure S1: Enrolment of patients with asthma among the Malaysian cohort of SABINA III. Patient population is described by practice type and asthma severity



One patient was excluded from the analysis because the duration of asthma was less than 12 months. SABA, short-acting β_2-agonist; SABINA, SABA use IN Asthma.

Figure S2: (A) SABA and ICS prescriptions in patients with mild asthma managed at primary and specialty care; B) SABA and ICS prescriptions in patients with moderate-to-severe asthma managed at primary and specialty care





ICS, inhaled corticosteroid; SABA, short-acting β_2-agonist; SABINA, SABA use IN Asthma.