How GINA recommendations solve real world problems in asthma

郭炳宏

臺大醫院內科部

GINA; since 1993 (WHO and NHIBL)

Global

INitiative for

Asthma

First GINA report: 1995 (184 pages)

GLOBAL INITIATIVE FOR ASTHMA

GLOBAL STRATEGY FOR
ASTHMA MANAGEMENT AND PREVENTION
NHLBI/WHO WORKSHOP REPORT

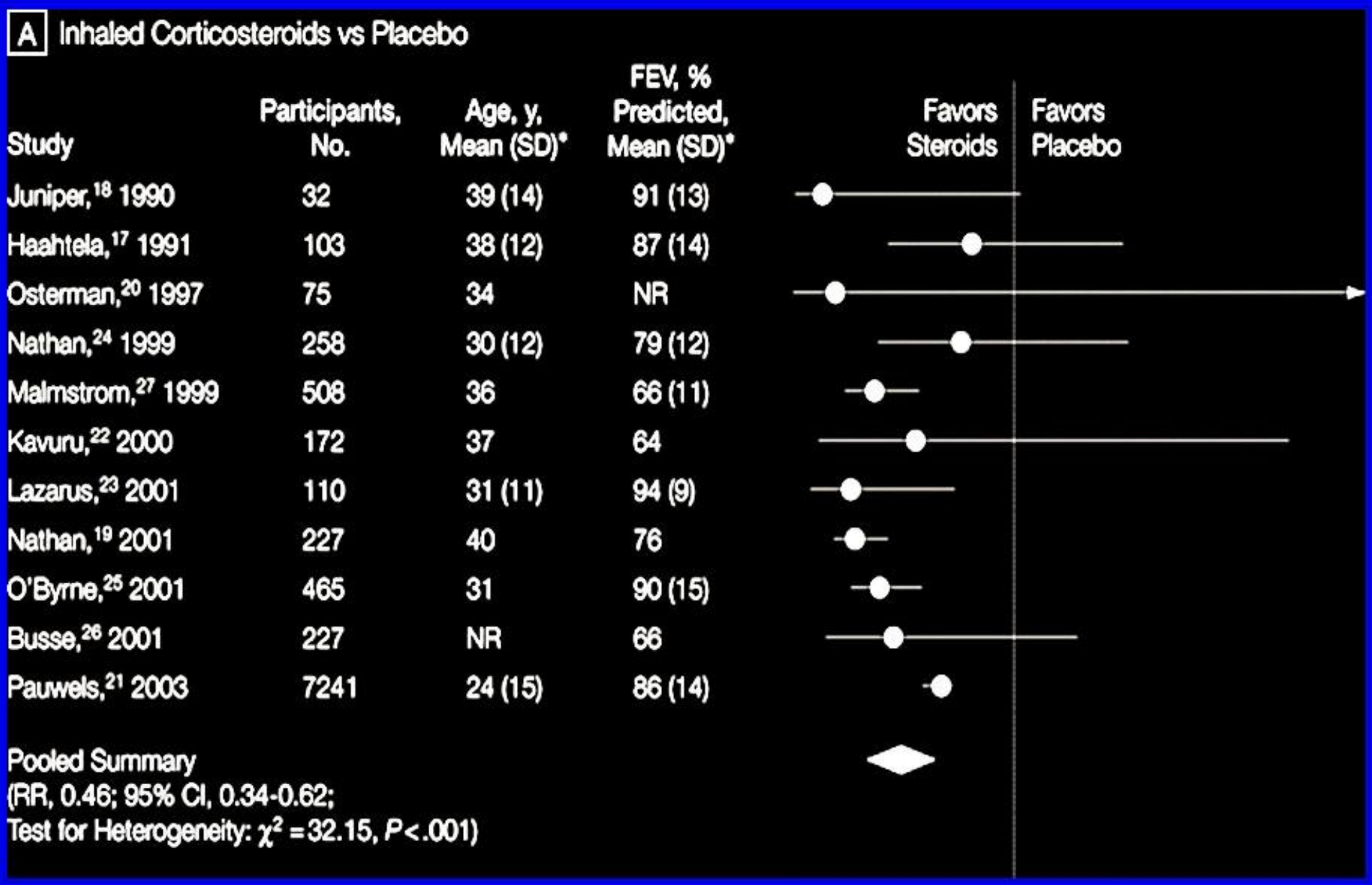
(Based on a March 1993 Meeting)

NATIONAL INSTITUTES OF HEALTH
National Heart, Lung, and Blood Institute
Publication Number 95-3659
January 1995
Reprinted May 1996

History of drug development for asthma

1965	Disodium cromoglycate (Intal)
1969	Salbutamol (Ventolin)
1972	Beclomethasone diproprionate (BDP) (Glaxo)
1984	Bambuterol (Bambec)
1992	Volmax
1993	Fluticasone (Flixotide)
1994	Salmeterol (Servent)
1996	Zafirlukast (Accolate)
1997	Formoterol (Oxis, Foradil)
1997	Budesonide
1998	Montelukast sodium (Singulair)
2000	FP/SM (Seretide)
2000	Beclomethasone HFA MDI (Qvar)
2001	BUD/FORM (Symbicort)
2003	Omalizumab (Xolair)

ICS vs placebo: 54% reduction in asthma exacerbations

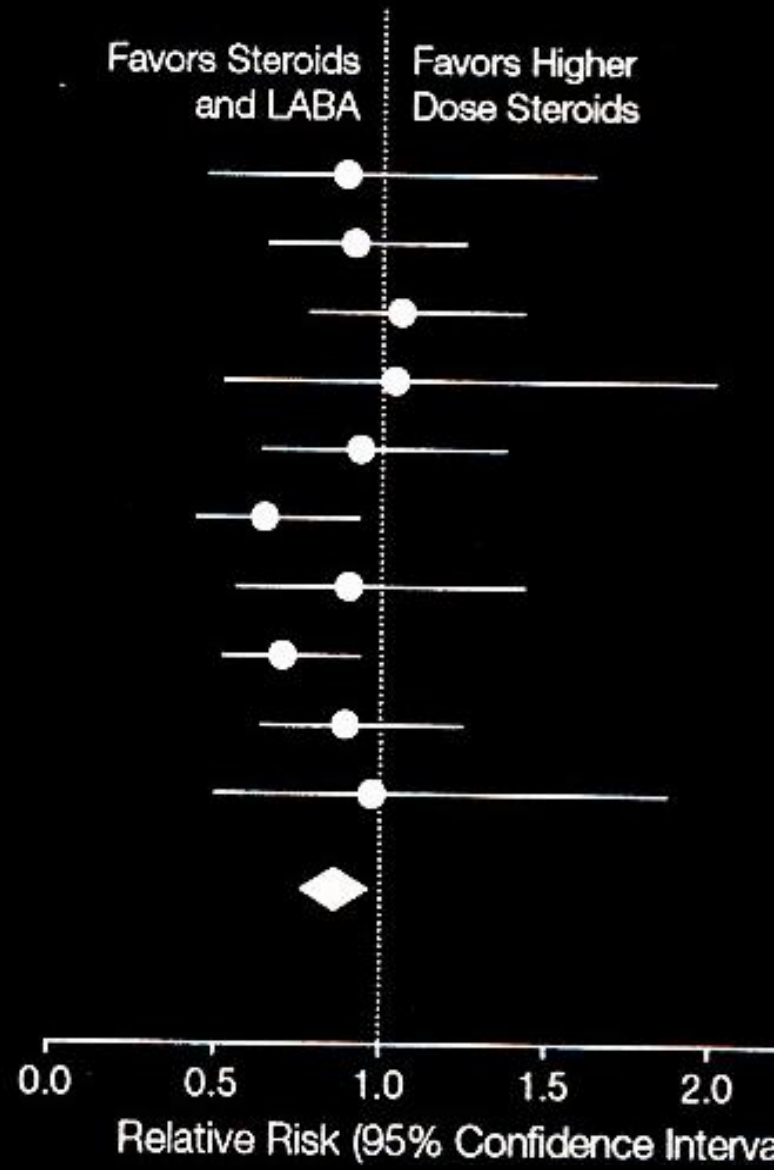


Sin et al, JAMA 2004; 292:367-376

ICS-LABA vs. ICS: 26% reduction in exacerbations

Study	Participants, No.	Age, y, Mean (SD)*	FEV, % Predicted, Mean (SD)*
Greening,[69] 1994	426	48 (16)	74 (19)
Woolcock,[71] 1996	738	44	73
Pauwels,[28] 1997	852	43	76
Van Noord,[70] 1999	274	47 (15)	72 (16)
Murray,[51] 1999	514	42 (13)	65 (10)
Matz,[65] 2001	925	37 (13)	61 (11)
Jenkins,[67] 2001	353	46	70
O'Byrne,[25] 2002	635	31	90 (15)
Ind,[29] 2003	496	45 (15)	2.3 (0.9) L†
Lalloo,[68] 2003	467	41	81

Pooled Summary
(RR, 0.86; 95% CI, 0.76-0.97;
Test for Heterogeneity: $\chi^2 = 6.88$, $P = .65$)



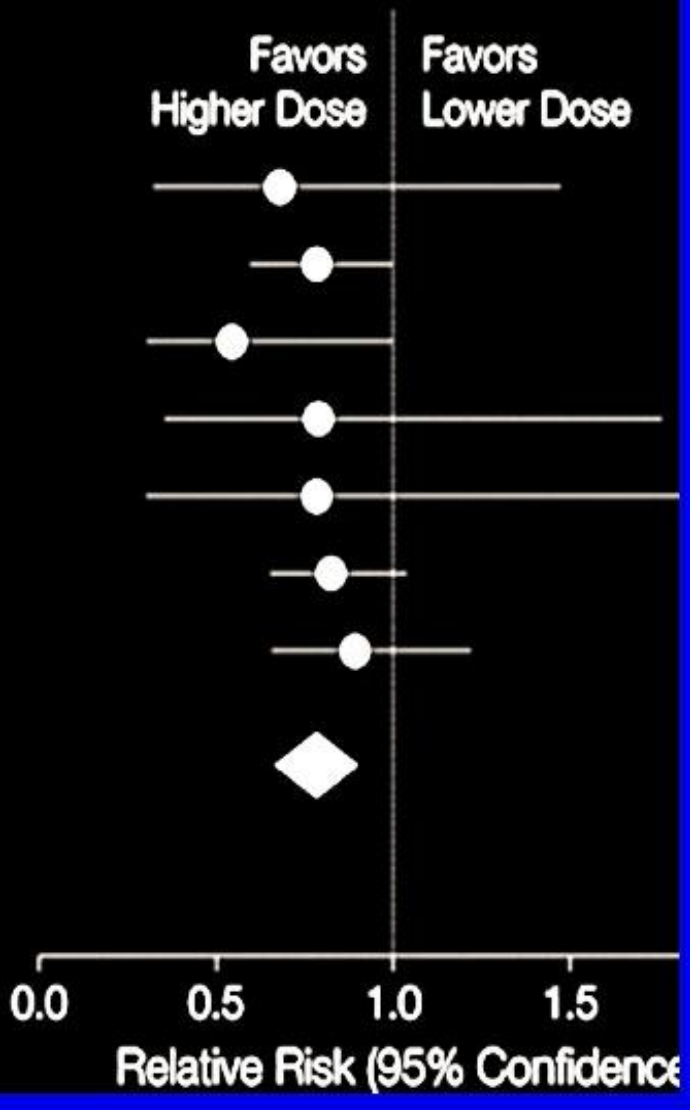
Sin et al, *JAMA* 2004; 292:367-376

Higher ICS dose: fewer exacerbations vs. lower dose

B Higher Dose vs Lower Dose Inhaled Corticosteroids

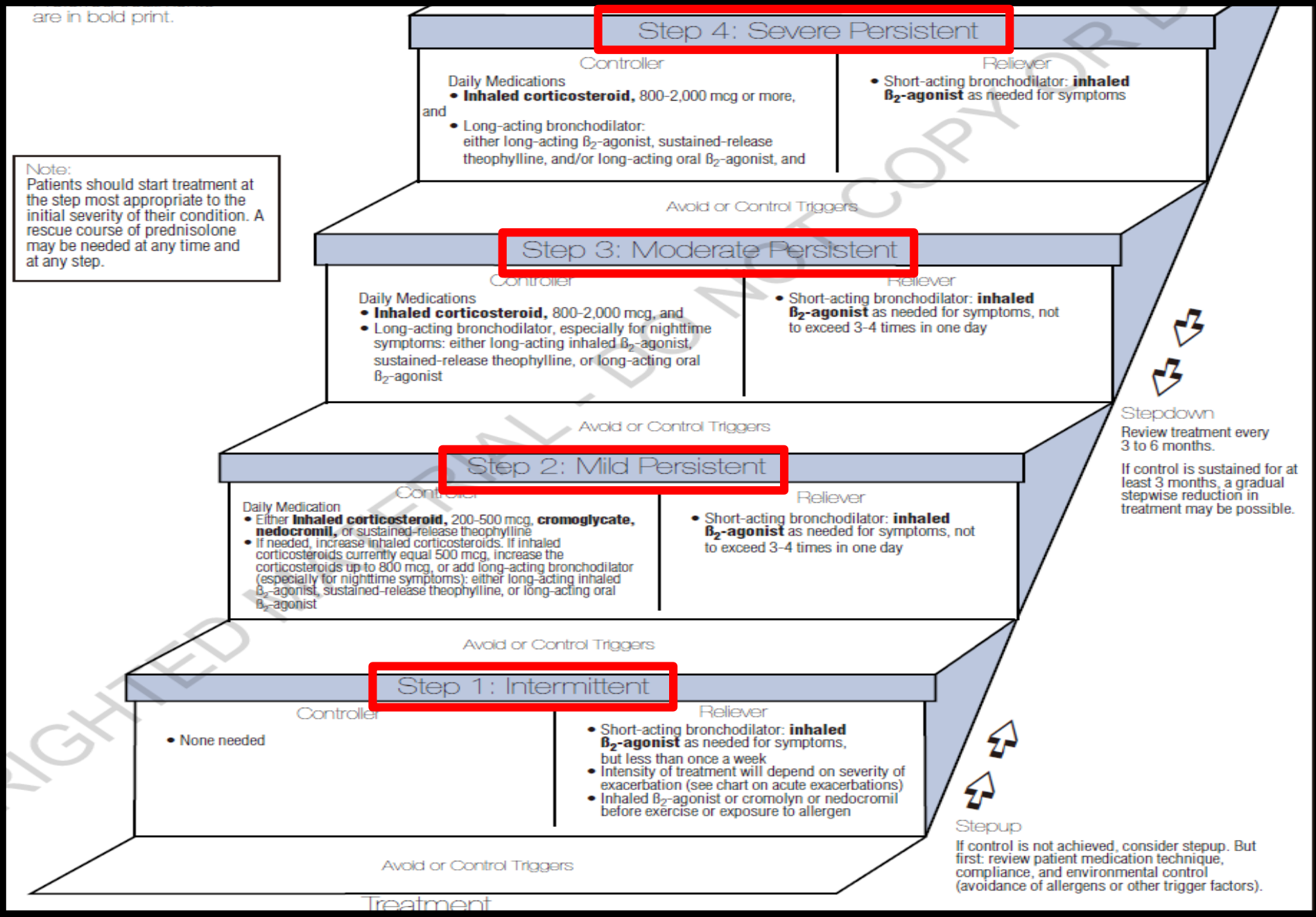
Study	Participants, No.	Age, y, Mean (SD)*	FEV, % Predicted, Mean (SD)*
Hummel,[31] 1992	142	43	NR
Pauwels,[28] 1997	427	43	76
Foresi,[30] 2000	142	38 (14)	74 (11)
Lim,[32] 2000	106	40 (14)	NR
Nathan,[19] 2001	113	40	76
O'Byrne,[25] 2001	629	37	86 (17)
Ind,[29] 2003	325	45 (15)	2.3 (0.9) L†

Pooled Summary
(RR, 0.77; 95% CI, 0.67-0.89;
Test for Heterogeneity: $\chi^2 = 2.81$, $P = .83$)

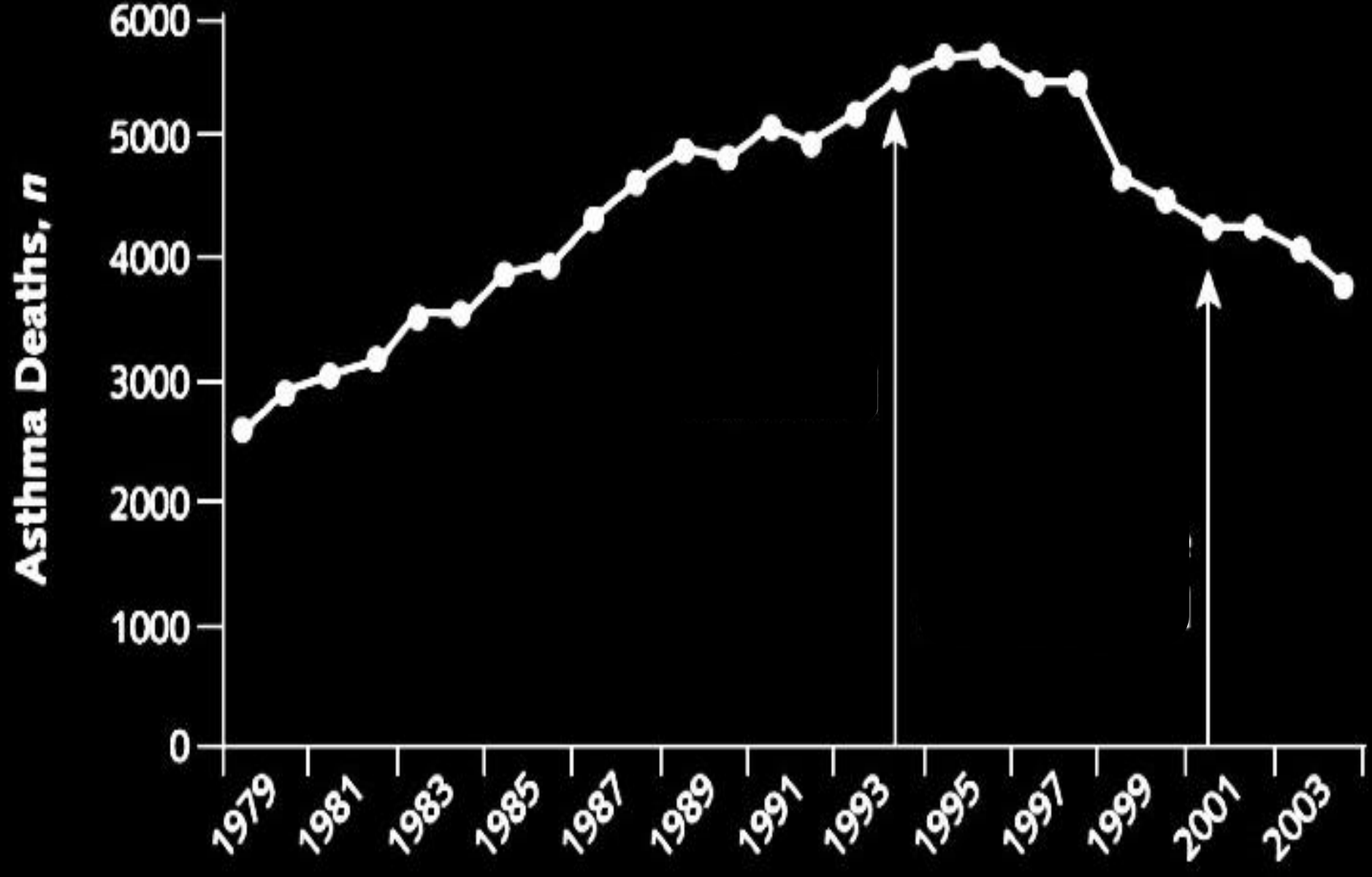


Sin et al, JAMA 2004; 292:367-376

GINA 1996 Stepwise Approach



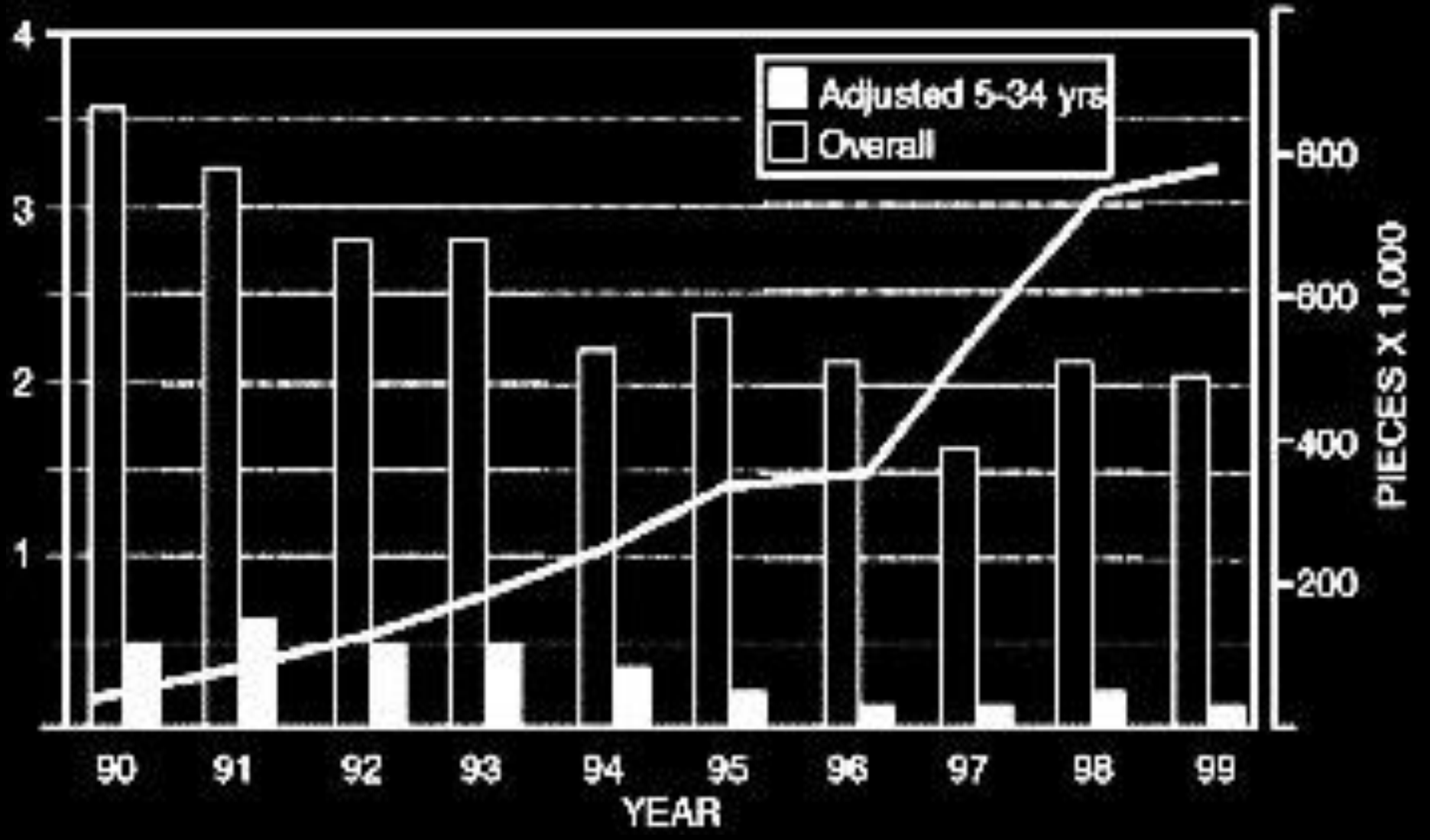
Asthma deaths in the US, 1979–2004



Nelson and Dorinsky, *Ann Intern Med* 2006;145:706

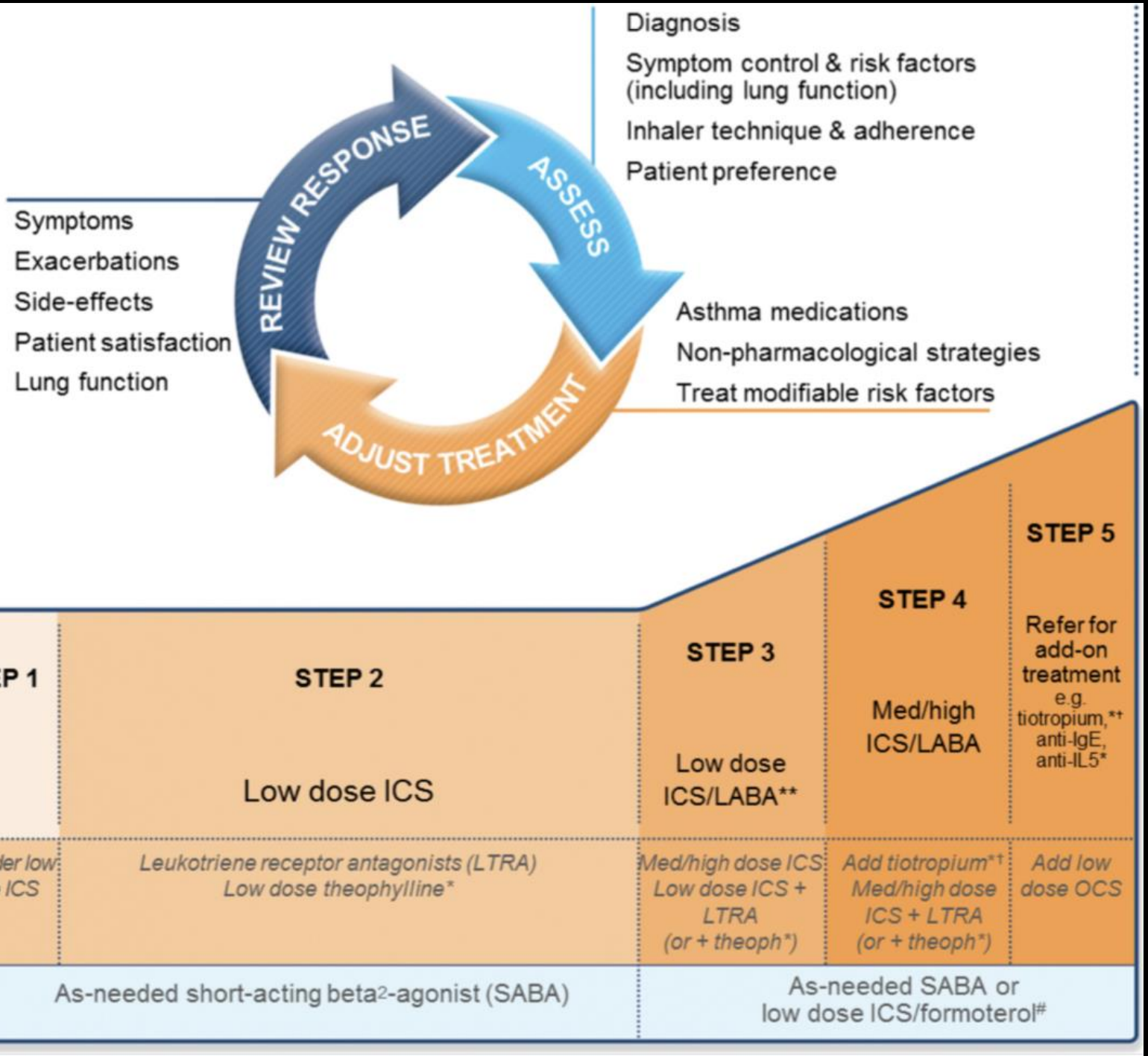
Argentina

ICS sales, asthma mortality and adjusted mortality



Neffen H, et al. Respir Med. 2006 Aug;100(8):1431-5

GINA 2018


Diagnosis
Symptom control & risk factors (including lung function)
Inhaler technique & adherence
Patient preference
REVIEW RESPONSE
ASSESS
ADJUST TREATMENT
Symptoms
Exacerbations
Side-effects
Patient satisfaction
Lung function
Asthma medications
Non-pharmacological strategies
Treat modifiable risk factors
PREFERRED CONTROLLER CHOICE
STEP 1
STEP 2
Low dose ICS
STEP 3
Low dose ICS/LABA**
STEP 4
Med/high ICS/LABA
STEP 5
Refer for add-on treatment e.g. tiotropium,*† anti-IgE, anti-IL5*
Other controller options
Consider low dose ICS
Leukotriene receptor antagonists (LTRA)
Low dose theophylline*
Med/high dose ICS
Low dose ICS + LTRA (or + theoph*)
Add tiotropium*†
Med/high dose ICS + LTRA (or + theoph*)
Add low dose OCS
RELIEVER
As-needed short-acting beta2-agonist (SABA)
As-needed SABA or low dose ICS/formoterol#

Reduce

GINA 2018 Asthma treatment

Increase

Step 1	Step 2	Step 3	Step 4	Step 5
	Low dose ICS	Low dose ICS/LABA	Med/High dose ICS/LABA	Add-on treatment Tiotropium Anti-IgE Anti-IL5
Consider low dose ICS	LTRA Low dose theophylline	Medium dose ICS, or Low dose ICS + LTRA (or + theophylline)	High dose ICS + Tiotropium or + LTRA (or + theophylline)	Add-on low dose oral corticosteroid

SABA prn

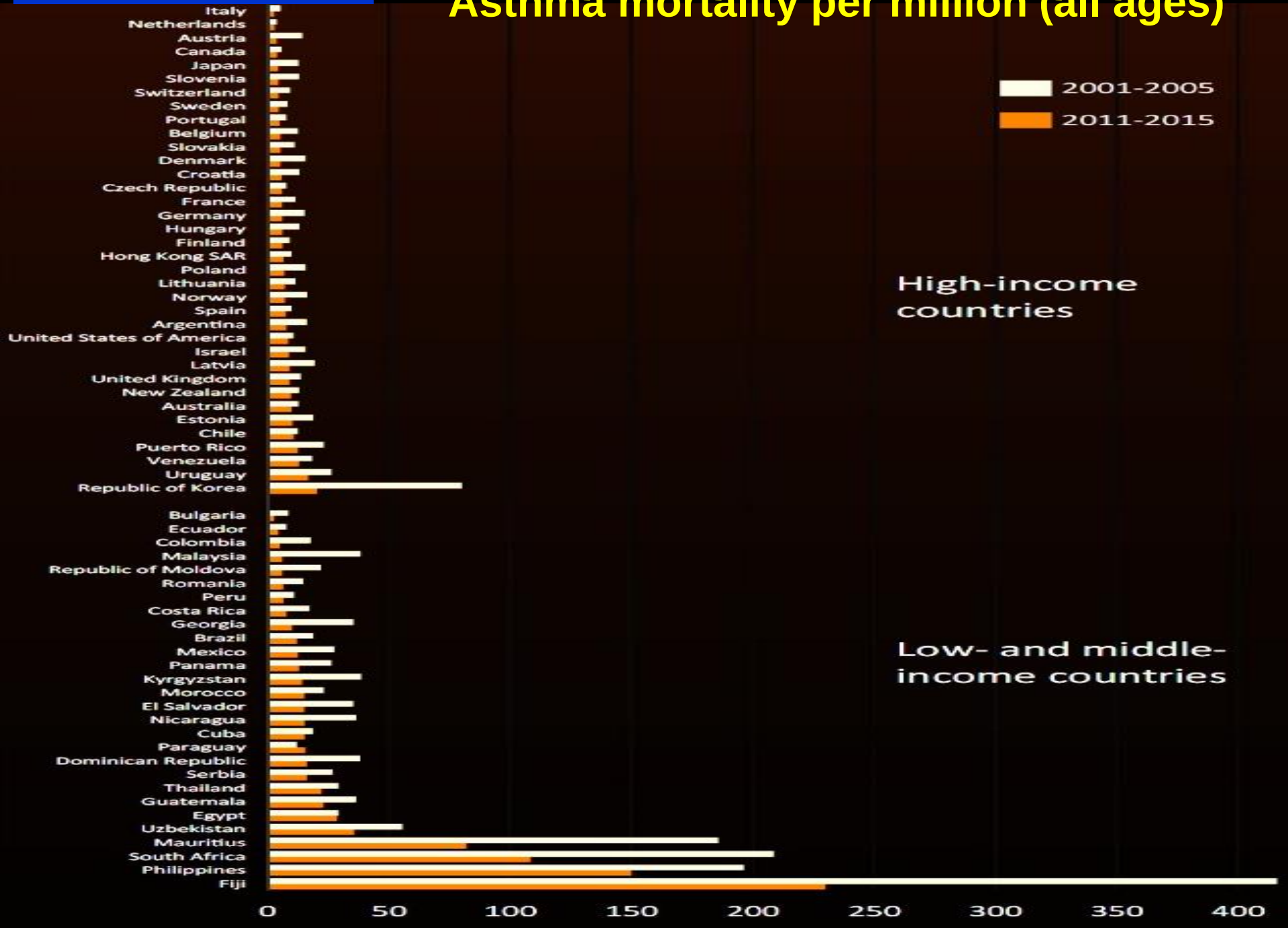
As-needed SABA or low-dose ICS/formoterol

The Global Asthma Report 2018

Global Asthma Network

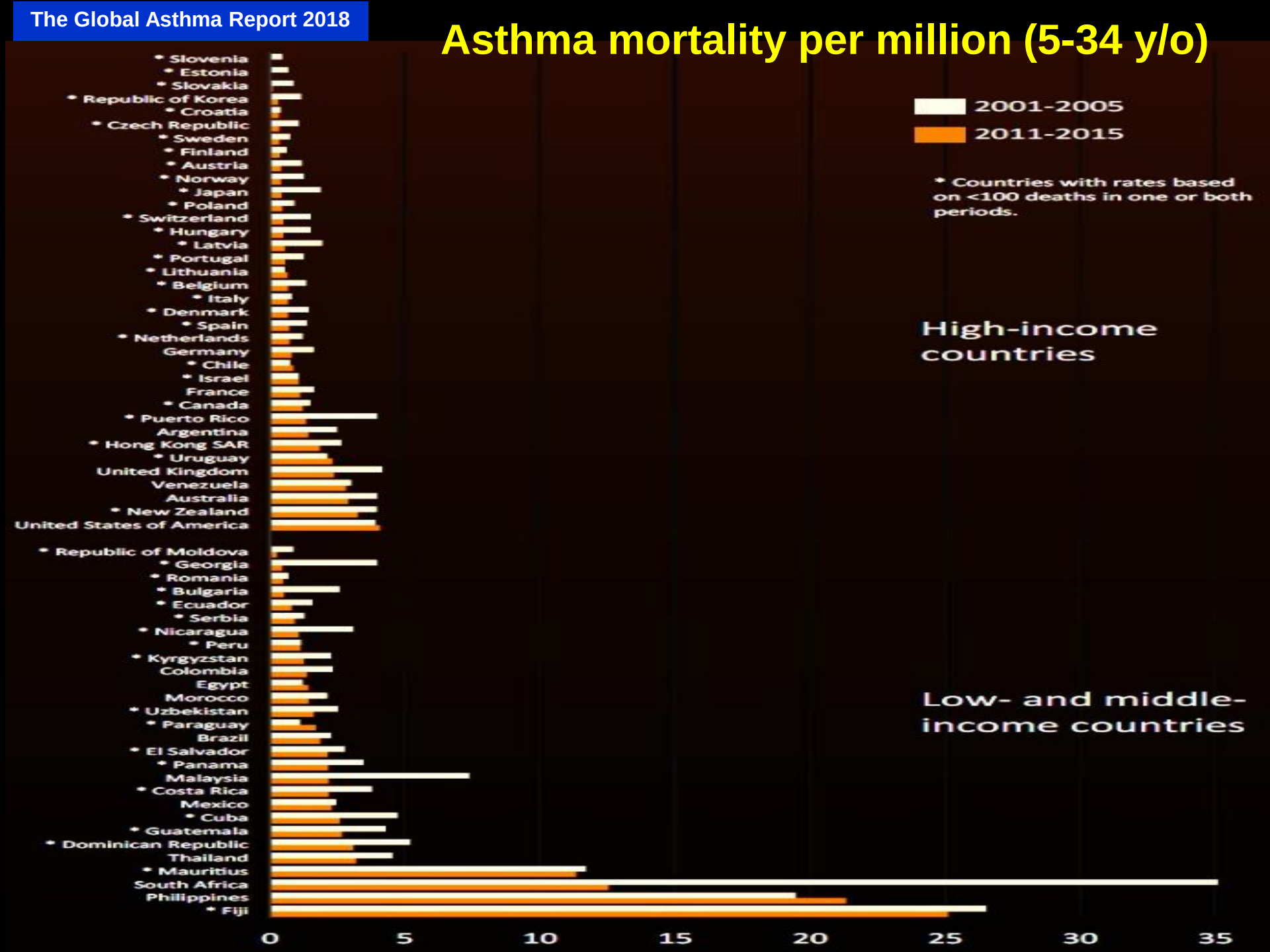
The Global Asthma Report 2018

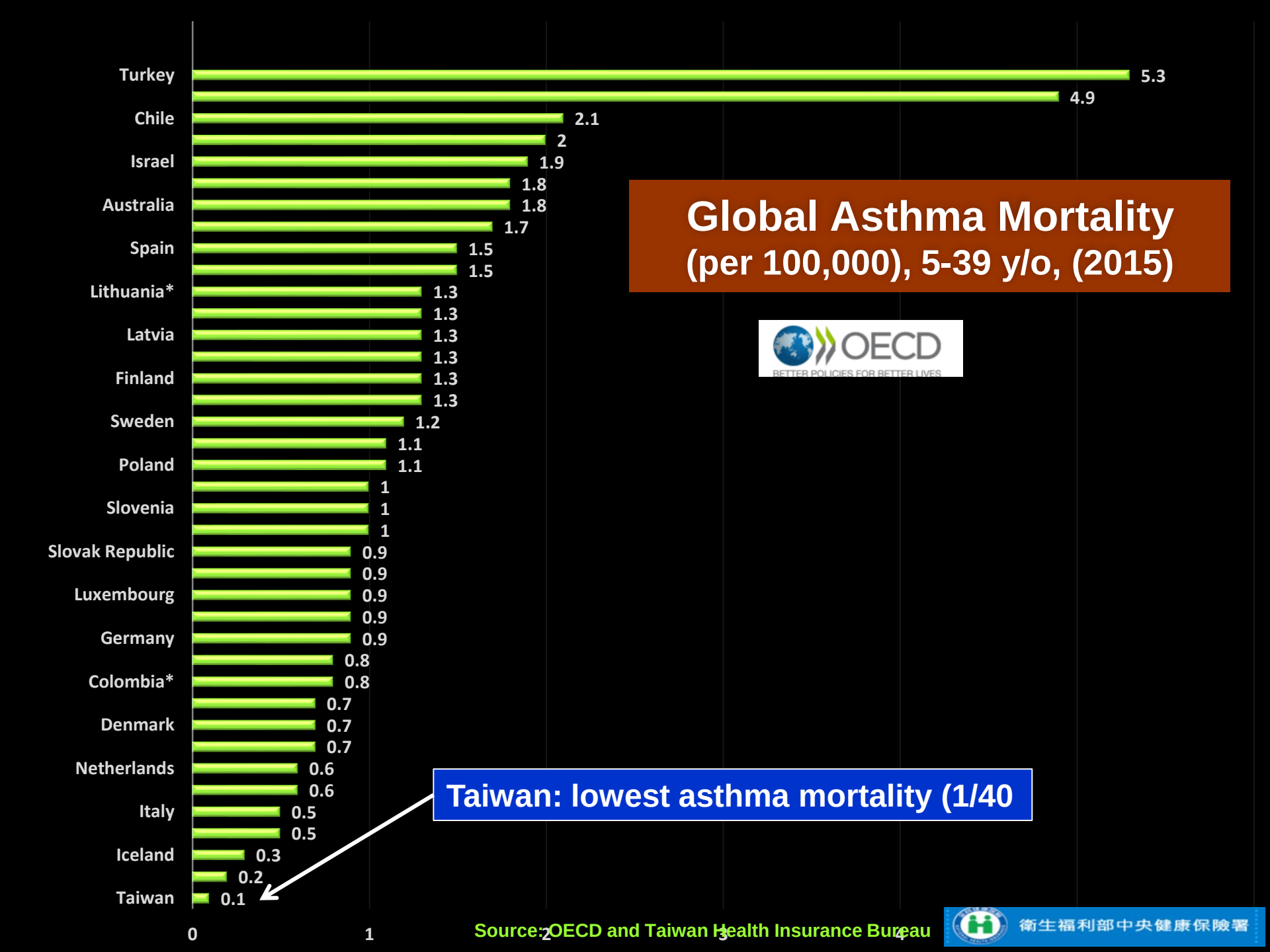
Asthma mortality per million (all ages)



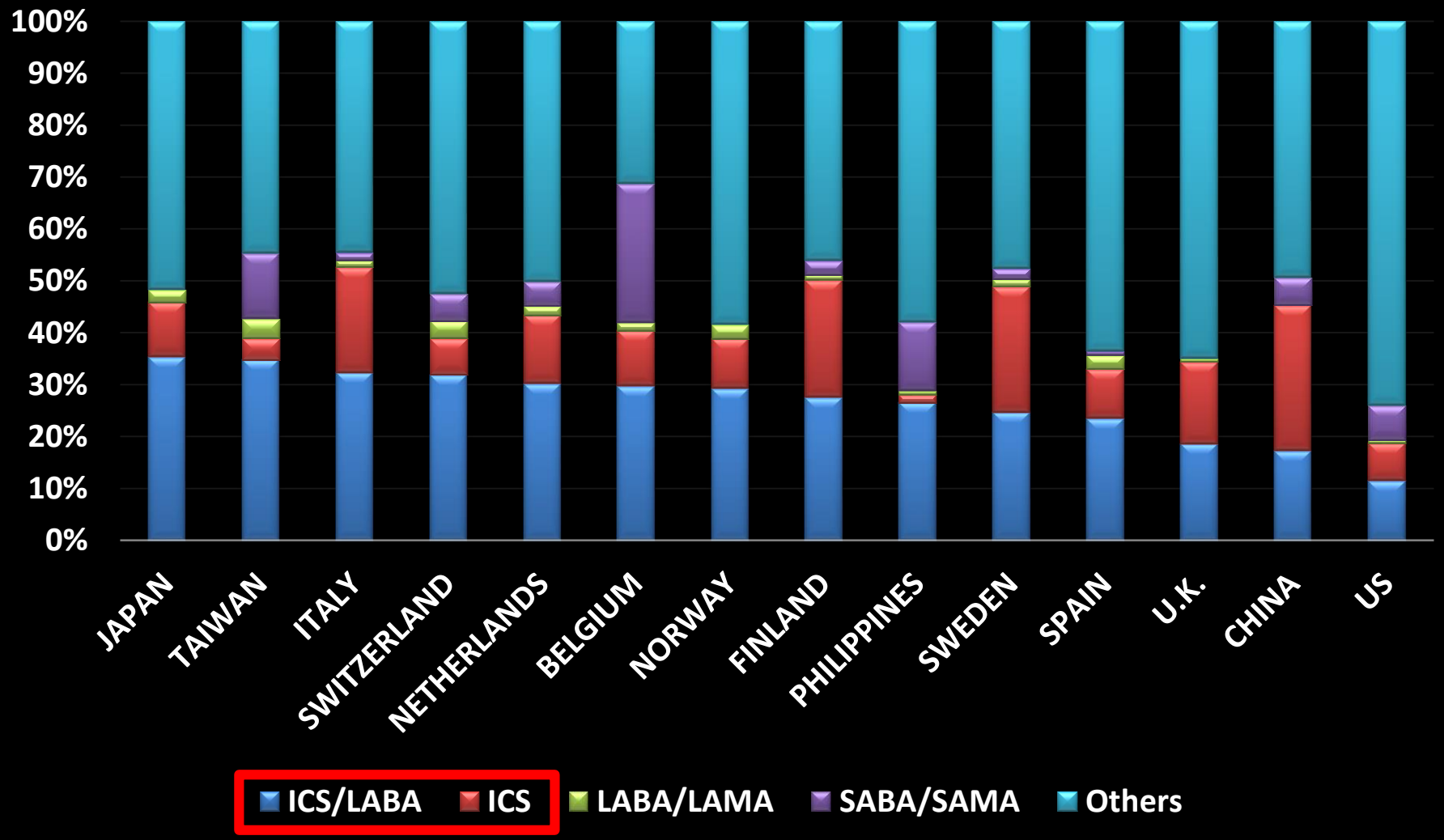
The Global Asthma Report 2018

Asthma mortality per million (5-34 y/o)




Global Asthma Mortality
(per 100,000), 5-39 y/o, (2015)
OECD
BETTER POLICIES FOR BETTER LIVES
Turkey 5.3
4.9
Chile 2.1
2
Israel 1.9
1.8
Australia 1.8
1.7
Spain 1.5
1.5
Lithuania* 1.3
1.3
Latvia 1.3
1.3
Finland 1.3
1.3
Sweden 1.2
1.1
Poland 1.1
1
Slovenia 1
1
Slovak Republic 0.9
0.9
Luxembourg 0.9
0.9
Germany 0.9
0.8
Colombia* 0.8
0.7
Denmark 0.7
0.7
Netherlands 0.6
0.6
Italy 0.5
0.5
Iceland 0.3
0.2
Taiwan 0.1
0
1
2
3
4
Taiwan: lowest asthma mortality (1/40
Source: OECD and Taiwan Health Insurance Bureau
衛生福利部中央健康保險署

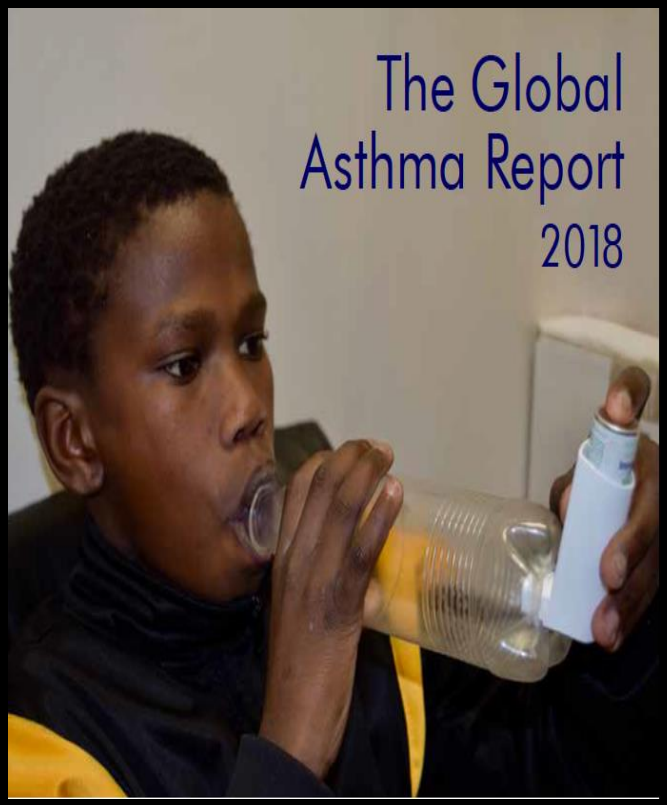
Global inhaler Market



Taiwan: top in the ICS/LABA vs. ICS ratio in the world

DATA SOURCES | IMS MAT AUG 2018 (pharmacy sales, retail & hospital where available). Volume is Counting Units. Data based on GLOBAL AZ Market Definition ETC Market.

Asthma: Still a serious global problem



- Affecting around 339 million patients in the world
- Still imposes an unacceptable burden on health care systems

GINA 2019
The Global Asthma Report 2018

USA CDC

Asthma attacks in the USA, N (%)

	Current asthma reported having ≥ asthma attacks, N (in thousands)	%
Total	11,462	45.6 %
Child (<18 years)	3,184	51.6 %
Adult (18+ years)	8,278	43.6

*Source: 2017 National Health Interview Survey (NHIS)

https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm

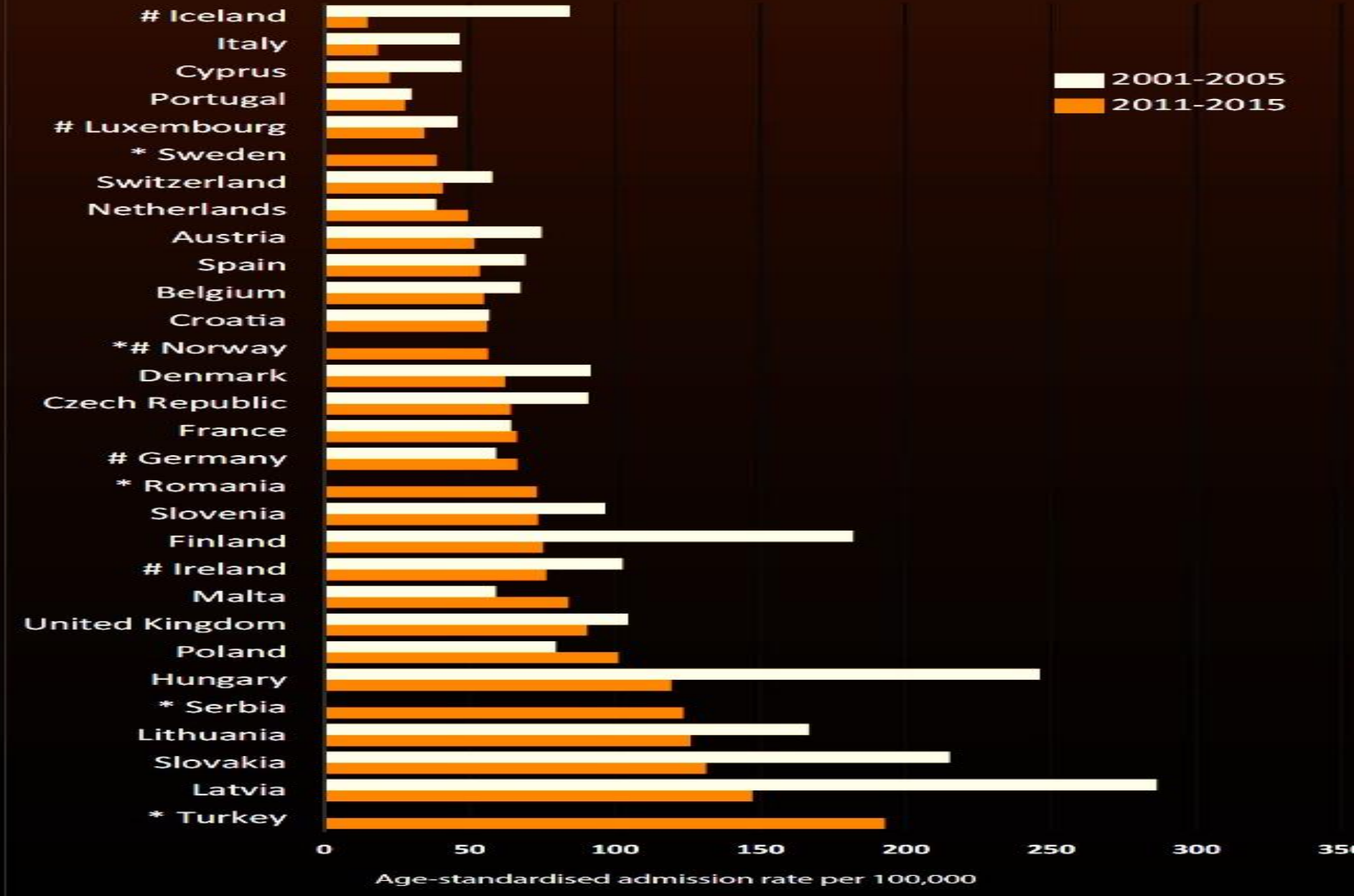
USA CDC

Healthcare use of asthmatics in USA (2016)

	Hospital Inpatient Stays		Emergency Department		Physician Office Visits	
	N	Rate	N	Rate	N	Rate
Total	188,968	5.9	1,776,851	55.9	9,789,350	307.8
Child (Age <18 y/o)	80,235	10.7	546,013	74.3	2,446,609	332.9
Adult (Age 18+ years)	108,505	4.4	1,230,838	50.3	7,342,741	300.3

https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm

Asthma admission rates in Europe



REALISE Asia

Asthma Control in Asia (GINA)

	REALISE EU	REALISE Asia	Taiwan
Controlled	20 %	18 %	20 %
Partially controlled	35 %	32 %	39 %
Uncontrolled	45 %	50 %	41 %

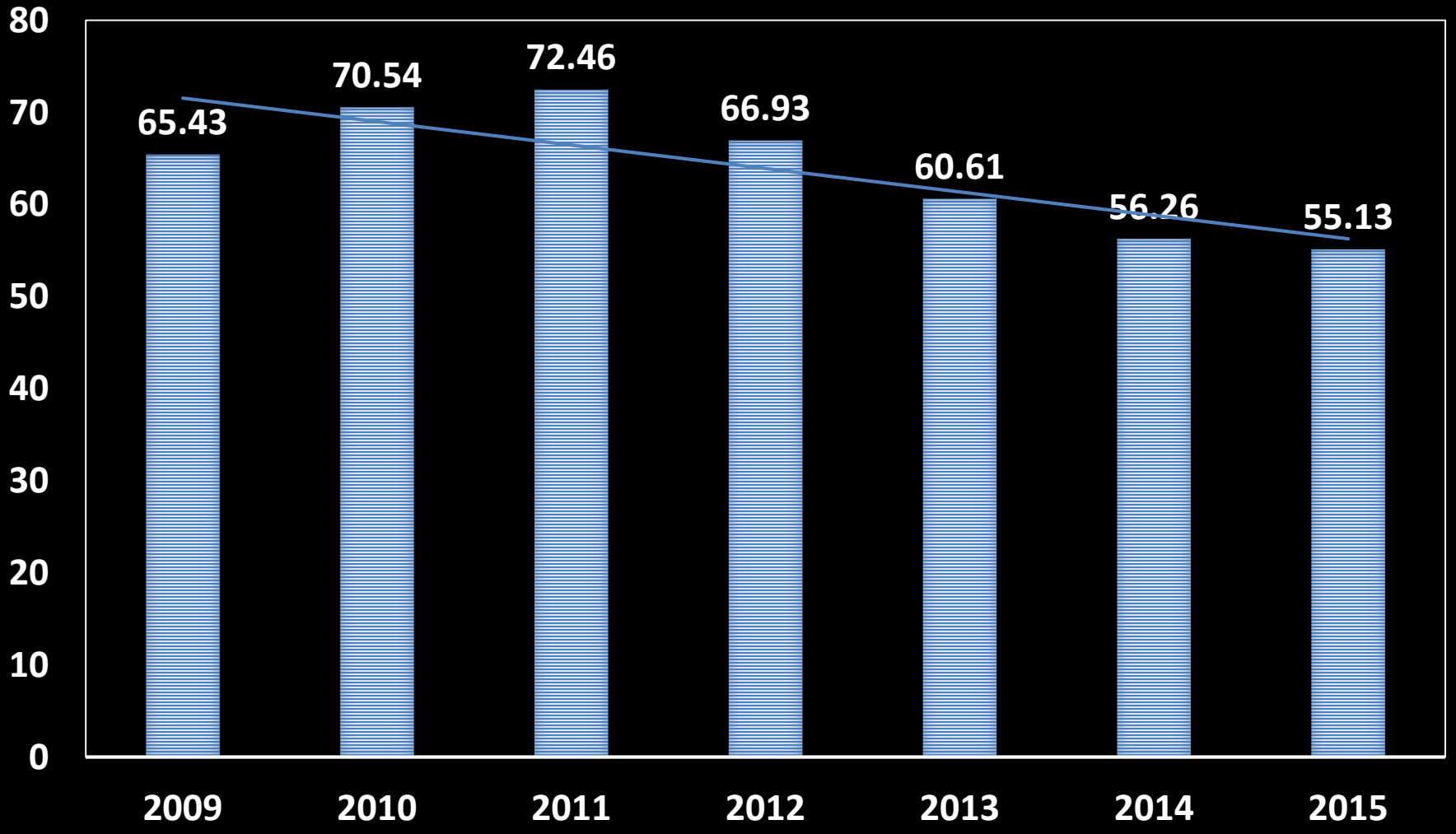
	Controlled	Partly controlled	Uncontrolled
% visited ER last year (N=947)	7%	20%	73%
% hospitalised last year (N=817)	3%	19%	78%
% used reliever medication for ≥2 times per week (n=673)	2%	13%	85%
% needed a course of steroid for worsening asthma (n=1,803)	11%	29%	60%

- 73% who visited the ER last year were uncontrolled

Chisholm A. NPJ Prim Care Respir Med. 2017 Jan 5;27:16089

Taiwan 2009-2015

Trend of Hospitalization rates of asthma in Taiwan (per 100,000)

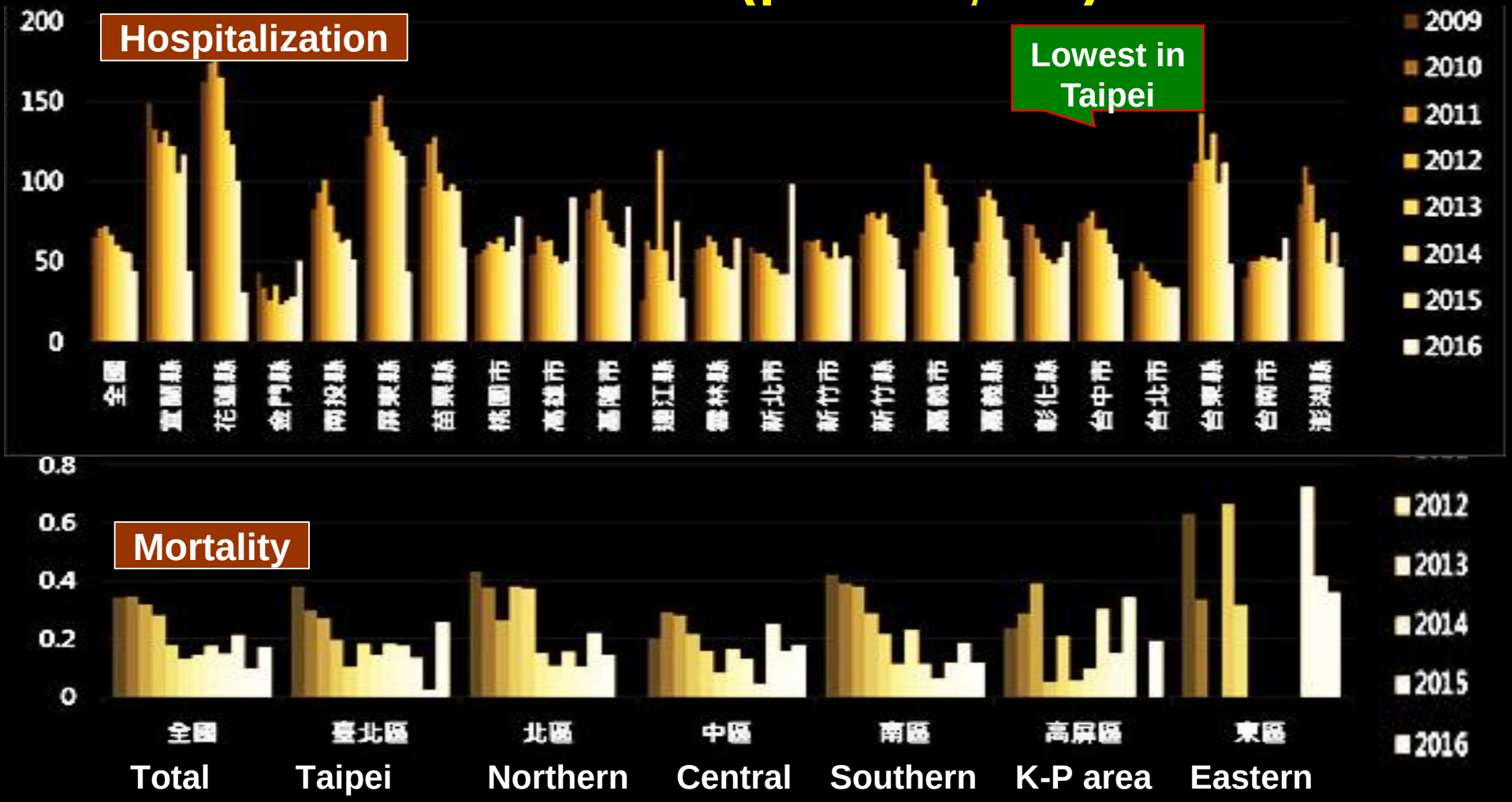


衛生福利部中央健康保險署

Source: Taiwan Health Insurance Bureau

Taiwan
2009-2016

Asthma hospitalization / mortality in Taiwan (per 100,000)



Asthma outcomes: worse in areas with lower socioeconomic status

衛生福利部中央健康保險署

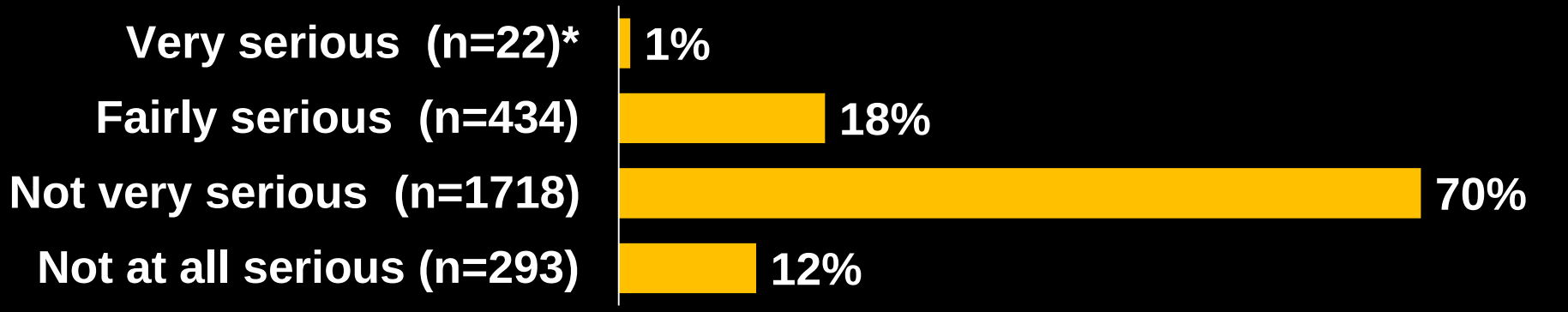
Source: Taiwan Health Insurance Bureau

Clinical scenario 1

- 49 y/o M, Hx: moderate allergic asthma
- 2019-10-19: ACT 24, Rx: Symbicort 2 IH bid & prn + Singular 1# hs
- 醫師: 最近情況怎麼樣？
- 病人: 還好. 不過一個月前感冒開始容易咳嗽, 有時有點胸悶, 但這星期有改善
- 醫師: 那你目前一天欣必擴吸幾個劑量？
- 病人: 早晚吸一個劑量. 上次醫師說夏天沒有症狀可減量
- 醫師: 不是有跟你交代氣喘有惡化就要增加劑量嗎？
- 病人：我只是感冒, 而且我只是容易咳嗽與胸悶, 應該沒有氣喘這個病吧！
- 醫師: ???

REALISE Asia

Perceived severity of asthma



Severity	REALISE Asia	Taiwan
Not at all severe	12 %	10 %
Not very severe	70 %	74 %
Fairly severe	18 %	15 %
Very severe	1 %	1 %

	REALISE Asia	REALISE EU
Ignored their condition to feel "normal"	60 %	43 %

- Asia: 82% perceive their asthma as NOT serious
- Taiwan: 74% considered their condition not serious

Chisholm A. NPJ Prim Care Respir Med. 2017 Jan 5;27:16089

Many patients with mild asthma don't think they have asthma

- China: 哮喘. Taiwan: 氣喘. Japan: 喘息

I just have chronic cough !

I don't have shortness of breath !!

I have never experienced wheezing !

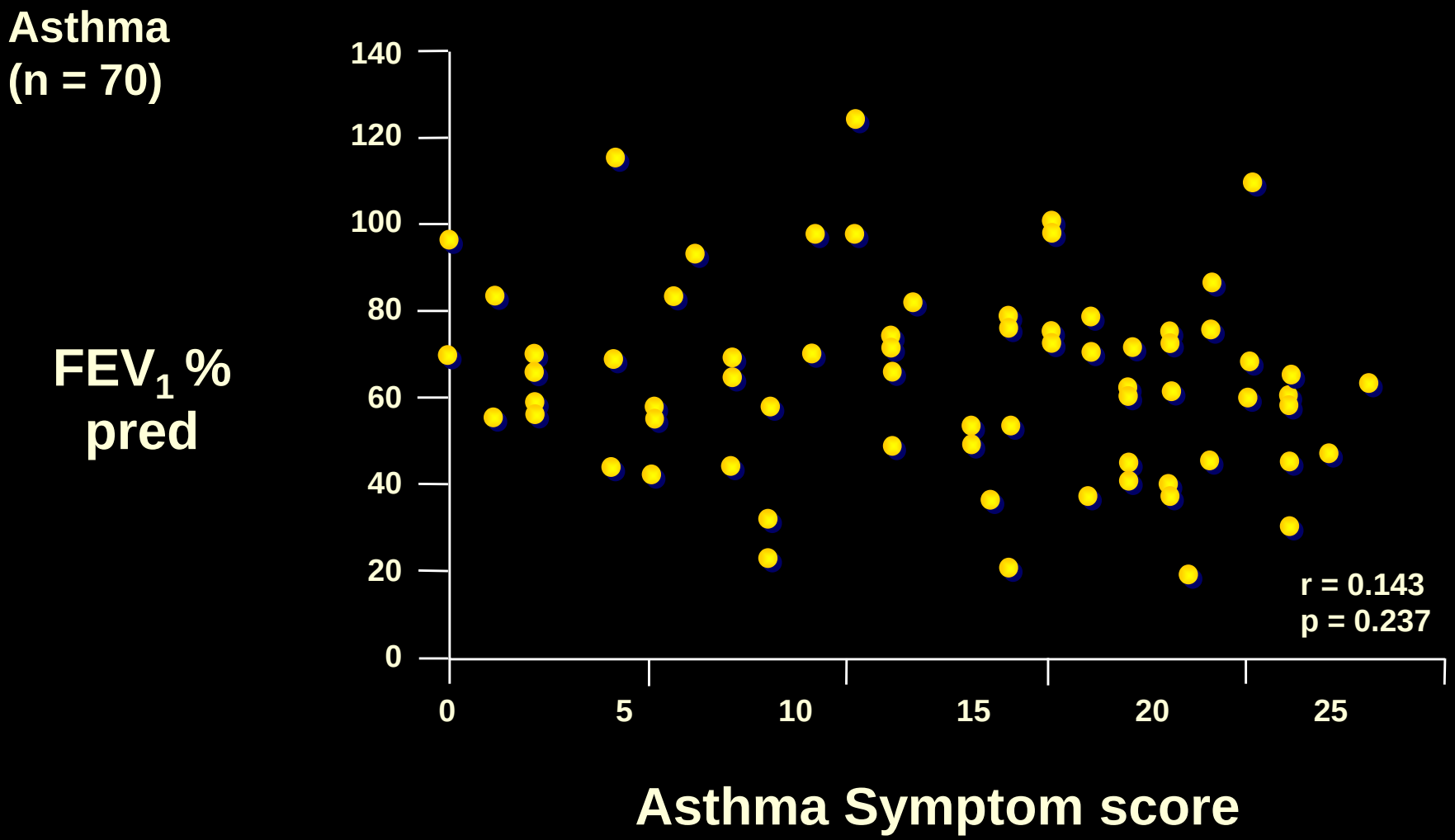
Cough

Chest tightness

SOB

Wheezing

Weak relation between FEV_1 and symptoms



Teeter JG et al.*Chest* 1998;113:272-277.

Definition of asthma

- GINA 2019: Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation, and is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation".

- Global Asthma Report 2018: Although not strictly a definition, this description captures the essential features for clinical purposes

Clinical scenario 2

36 y/o F, Hx: mild to moderate asthma. Rx: Symbicort 1-2 IH bid, prn

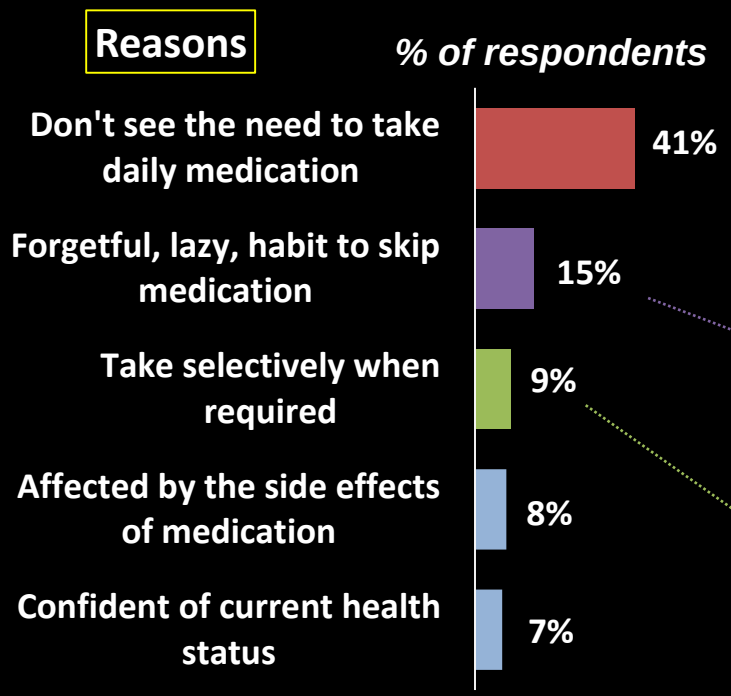
- 醫師: 最近情況怎麼樣？
- 病人: 還好, 不過能不能開一支急救用藍色吸入器給我?
- 醫師: 最近常用備勞喘嗎？
- 病人: 兩個月前感冒開始容易咳嗽, 有時有點胸悶.
- 醫師: 那妳有規則吸欣必擴嗎？
- 病人: 不好意思, 最近太忙, 常常忘記吸藥.

- 醫師:是哦...那為什麼妳每天絕對不會忘記為妳的手機充電？

REALISE Asia

Primary reason not taking medication every day: do not see a need (41%) (no attacks or symptoms)

47% disagree that they need to take controller inhaler regularly to control their asthma well



"Feel I am still alright and there is no need" –, CN
"Because I don't experience asthma attacks every day." – INDO

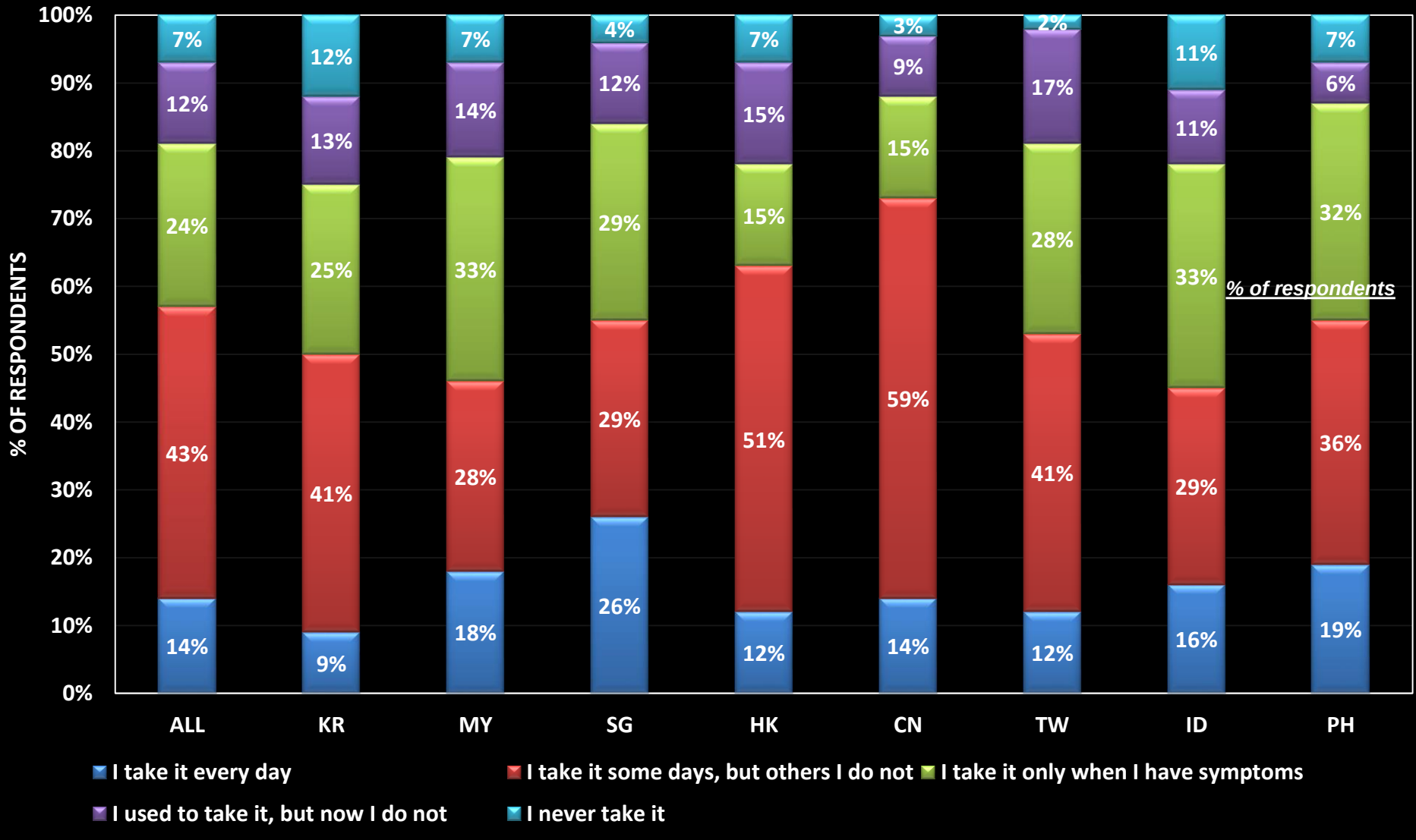
"Sometimes I'm busy with work so I forgot." – CN

"I only take it when I have attacks." – PH

Chisholm A. NPJ Prim Care Respir Med. 2017 Jan 5;27:16089

REALISE Asia (2014)

Controller use in Asia



Only 14% asthmatics in Asia take ICS everyday (Taiwan: 12%)

Chisholm A. NPJ Prim Care Respir Med. 2017 Jan 5;27:16089

China 2015

Controller adherence in mild asthma

Disease burden of mild asthma in China

Bo DING[1] AND Mark SMALL[2]

- 9 cities in China: Beijing, Chengdu, Guangzhou, Jinan, Nanjing, Shanghai, Shenyang, Wuhan and Xi'an

	Overall (n = 229)	Step 1 (25.3 %)	Step 2 (74.7 %)
Low-dose ICS	37 (16.2)	0 (0.0)	37 (21.6)
LTRA monotherapy	87 (38.0)	0 (0.0)	87 (50.9)
Xanthine monotherapy	47 (20.5)	0 (0.0)	37 (21.6)
High adherence	29 (12.7)	6 (10.3)	23 (13.5)

- **High adherence: only 12.7 %**

Ding B, Small M, Respirology 2018; 23: 369–377

REALISE Asia

Use of Reliever Inhaler in Asia

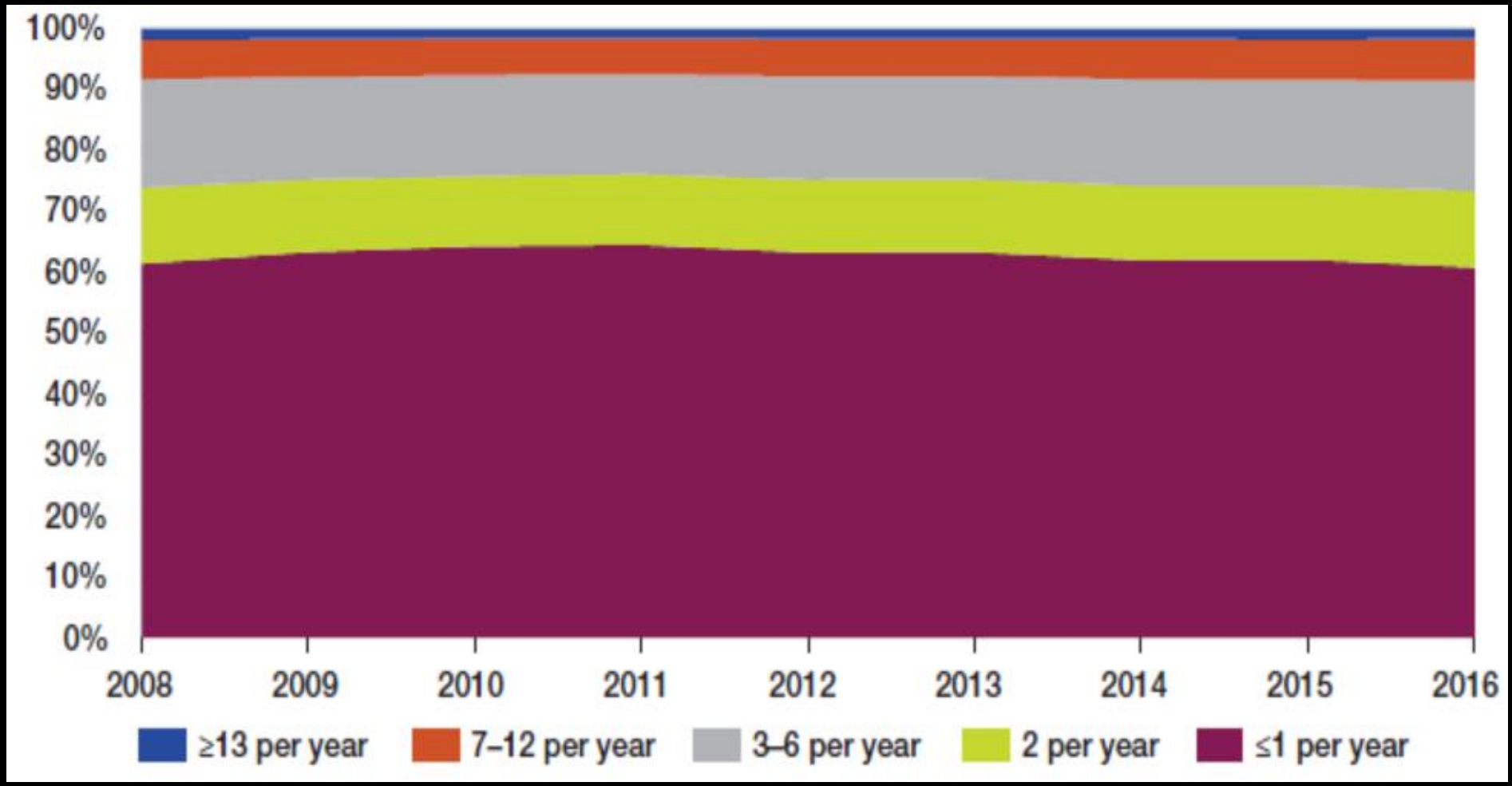
Controller use	REALISE Asia	Taiwan
Do you have a reliever ?		
Yes		72 %
No		28 %
(For those with relievers) The number of reliever used in the last week :		
0		28 %
1-3		53 %
4-6		12 %
7-10		7 %

- Reliever use: 2.1 times per week

Chisholm A. NPJ Prim Care Respir Med. 2017 Jan 5;27:16089

SABINA UK

% Mild asthma patients receiving SABA prescriptions (2008 – 2016)



- >1/3 of patients were prescribed SABA ≥3 canisters per year
- SABA prescriptions have not changed over the past decade.

Chloe I. Bloom et al. ERS 2019, Madrid, Spain

SABINA UK

% of patients changing SABA and ICS

Treatment	% increasing SABA	% decreasing SABA	% remaining the same
SABA alone	4.9	4.6	90.5
Low-dose ICS + SABA	12.3	11.7	74.1

- Around 1/4 of patients on low-dose ICS increased or decreased the frequency of their SABA use.
- Mean ICS daily dose changed only in <0.5% of patients
- More variability year-to-year in SABA than ICS prescribing → SABA use is changed rather than ICS in response to changes in asthma symptom control

Chloe I. Bloom et al. ERS 2019, Madrid, Spain

HERA

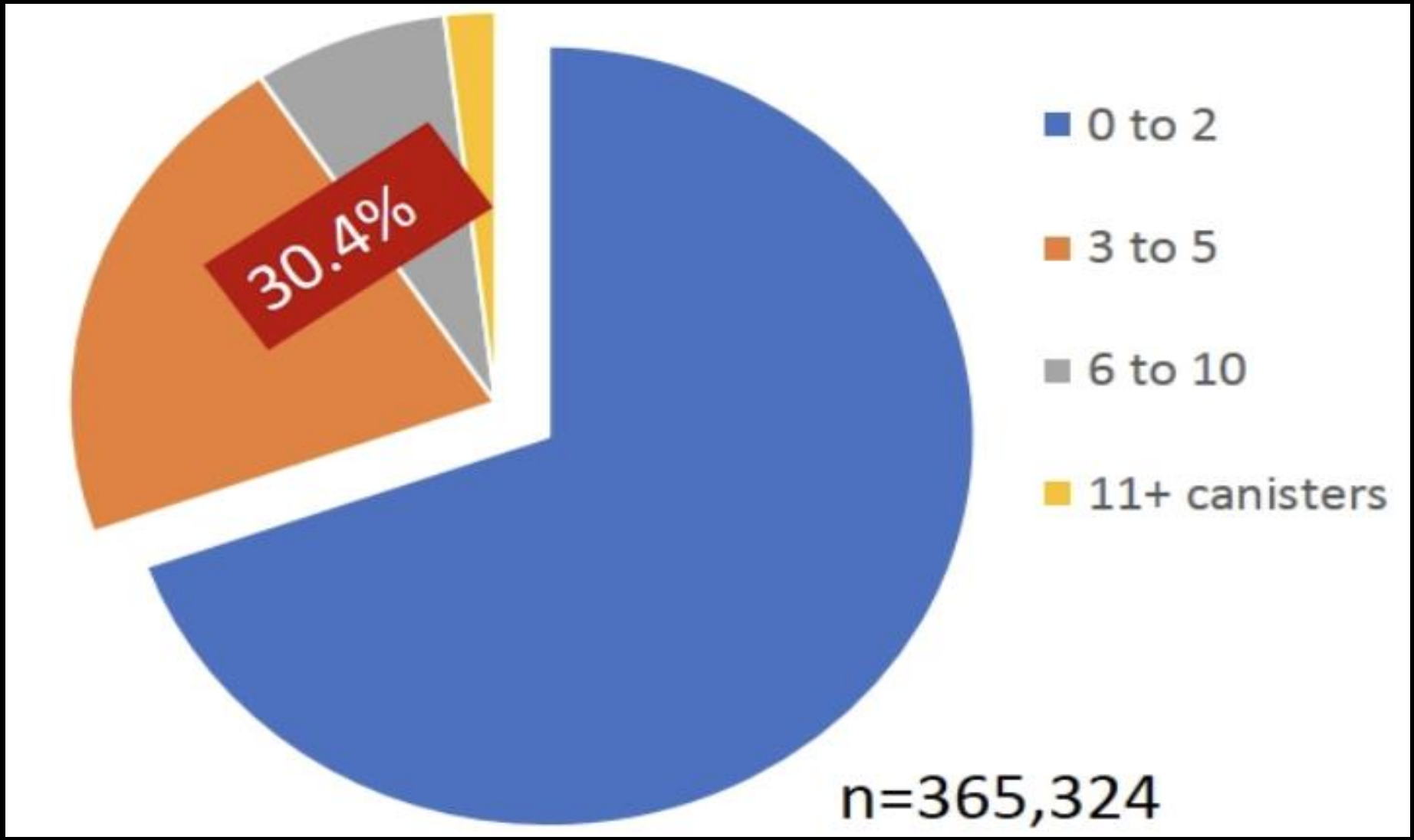
Are SABA-reliant asthma patients receiving adequate ICS therapy?
A nationwide cohort study in Sweden

- N = 365,324
- mean age 27.6 years
- 55% women
- 30.4% collected ≥ 3 SABA canisters during the baseline year: 其中 28.9% had no collection of ICS,

Ekstrom M et al. ERSA Congress, 2019, Madrid

HERA

SABA use at baseline



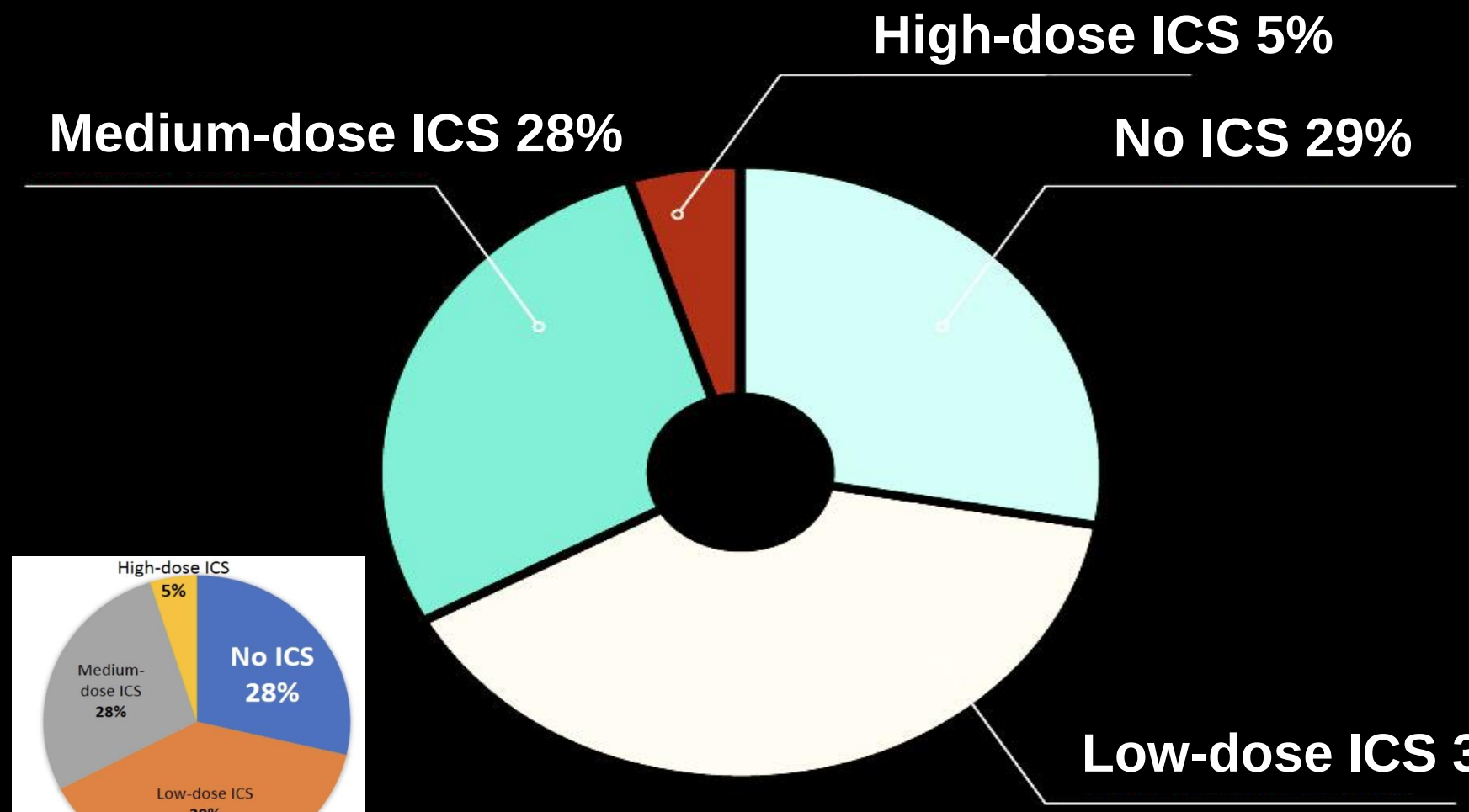
30.4% : SABA canisters ≥ 3 per year

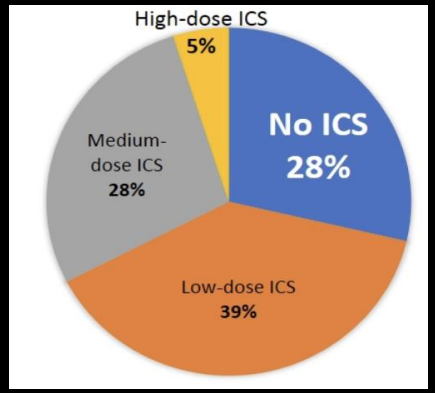
Ekstrom M et al. ERSA Congress, 2019, Madrid

Ekstrom M et al. ERSA Congress, 2019, Madrid

HERA

ICS therapy in asthma patients overusing SABA (≥ 3 canisters/year)





Ekstrom M et al. ERSA Congress, 2019, Madrid

HERA

Baseline characteristics for SABA overusing (≥ 3 canisters/yr) patients by ICS use (n = 109,438)

	No ICS (29%)	Low-dose ICS (39%)	Medium-dose ICS (28%)	High-dose ICS (5%)
Female, n (%)	16,084 (50.7)	23,853 (55.5)	15,997 (52.2)	2795 (51.2)
Age, mean (SD)	28.3 (10.7)	28.9 (10.8)	25.4 (11.7)	25.0 (11.7)
Any exacerbation during baseline year, n (%)	3510 (11.1)	8770 (20.4)	7009 (22.9)	1585 (29.0)
Hospitalization / 1000PY	0.9 (0.6 – 1.2)	4.1 (3.5 – 4.8)	7.0 (6.1 – 8.0)	15.2 (11.9 – 18.5)
Outpatient visits / 1000PY	39.7 (37.5 – 41.9)	199.0 (194.8 – 203.2)	349.2 (342.6 – 355.8)	492.9 (474.2 – 511.5)
Collected medication, n (%)				
LABA	789 (2.5)	3649 (8.5)	3455 (11.3)	855 (15.7)
Leukotriene modifiers	784 (2.5)	3814 (8.9)	4518 (14.7)	1324 (24.3)
Oral corticosteroids	3495 (11.0)	8695 (20.2)	6944 (22.7)	1569 (28.7)
Anticolinergics	51 (0.2)	142 (0.3)	134 (0.4)	54 (1.0)
N-acetylcysteine	1068 (3.4)	2862 (6.7)	2053 (6.7)	531 (9.7)
Antibiotics	3477 (11.0)	6957 (16.2)	4736 (15.4)	1070 (19.6)
Antihistamines	9608 (30.3)	18,480 (43.0)	13,647 (44.5)	2421 (44.4)
Nasal corticosteroids	5754 (18.1)	13,225 (30.8)	9507 (31.0)	1799 (33.0)

Ekstrom M et al. ERSA Congress, 2019, Madrid

HERA

Risk of exacerbation by ICS use

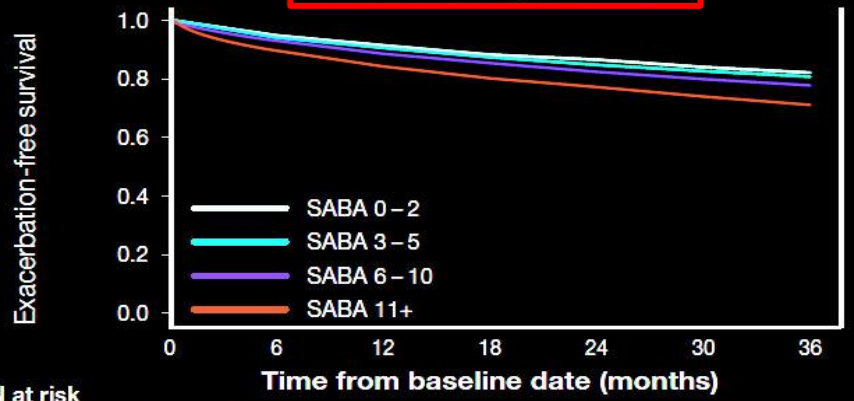
Baseline SABA use	Adjusted*, HR (95% CI)
No ICS	
≤2 canisters	1.00
3 – 5 canisters	1.12 (1.09 – 1.16)
6-10 canisters	1.26 (1.20 – 1.32)
11+ canisters	1.48 (1.37 – 1.60)
Low-dose ICS	
≤2 canisters	1.00
3 – 5 canisters	1.30 (1.27 – 1.33)
6 – 10 canisters	1.45 (1.40 – 1.49)
11+ canisters	1.73 (1.64 – 1.82)
Medium-dose ICS	
≤2 canisters	1.00
3 – 5 canisters	1.34 (1.31 – 1.38)
6 – 10 canisters	1.54 (1.49 – 1.60)
11+ canisters	2.01 (1.89 – 2.13)
High-dose ICS	
≤2 canisters	1.00
3 – 5 canisters	1.41 (1.32 – 1.50)
6 – 10 canisters	1.75 (1.61 – 1.90)
11+ canisters	2.12 (1.89 – 2.39)

Ekstrom M et al. ERSA Congress, 2019, Madrid

HERA

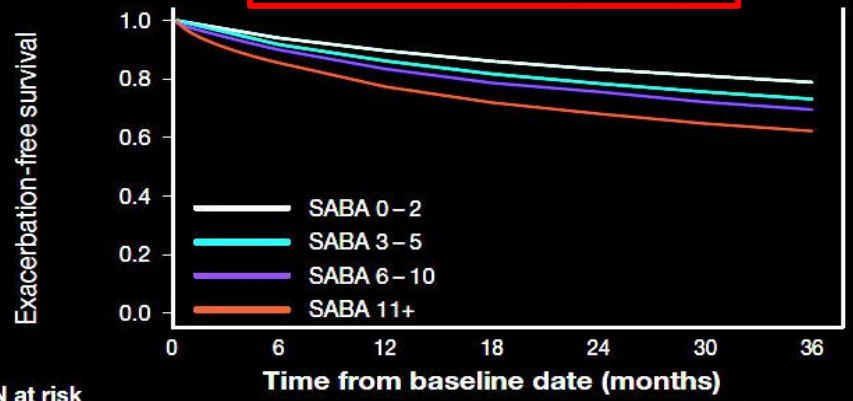
Exacerbation risk and mortality: increased with collected SABA canisters at baseline

No ICS during baseline



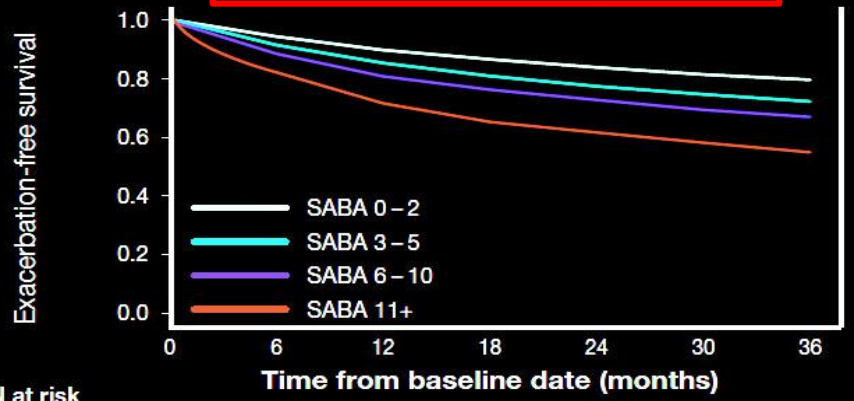
N at risk							
SABA 0 – 2	68850	65384	62891	57945	52749	49081	44842
SABA 3 – 5	23368	22077	21141	19837	18498	17461	16441
SABA 6 – 10	6625	6171	5872	5530	5213	4944	4694
SABA 11+	1744	1566	1463	1380	1313	1249	1180

Low-dose ICS during baseline



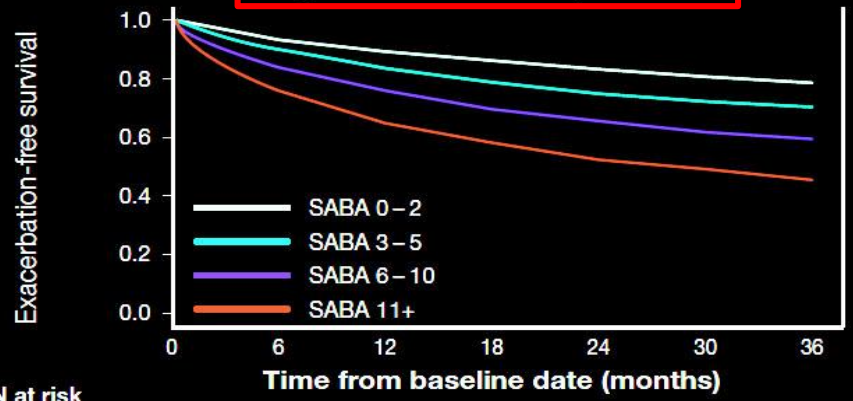
N at risk							
SABA 0 – 2	106952	100621	95841	88986	81808	76775	71137
SABA 3 – 5	29136	26709	25065	23149	21398	20078	18769
SABA 6 – 10	11014	9910	9203	8510	7972	7474	7061
SABA 11+	2823	2411	2183	1999	1866	1760	1666

Medium-dose ICS during baseline



N at risk							
SABA 0 – 2	67793	63858	60917	56383	51582	48304	44543
SABA 3 – 5	20655	18891	17651	16166	14752	13737	12709
SABA 6 – 10	7956	7021	6437	5913	5433	5076	4716
SABA 11+	2045	1680	1465	1322	1216	1135	1052

High-dose ICS during baseline

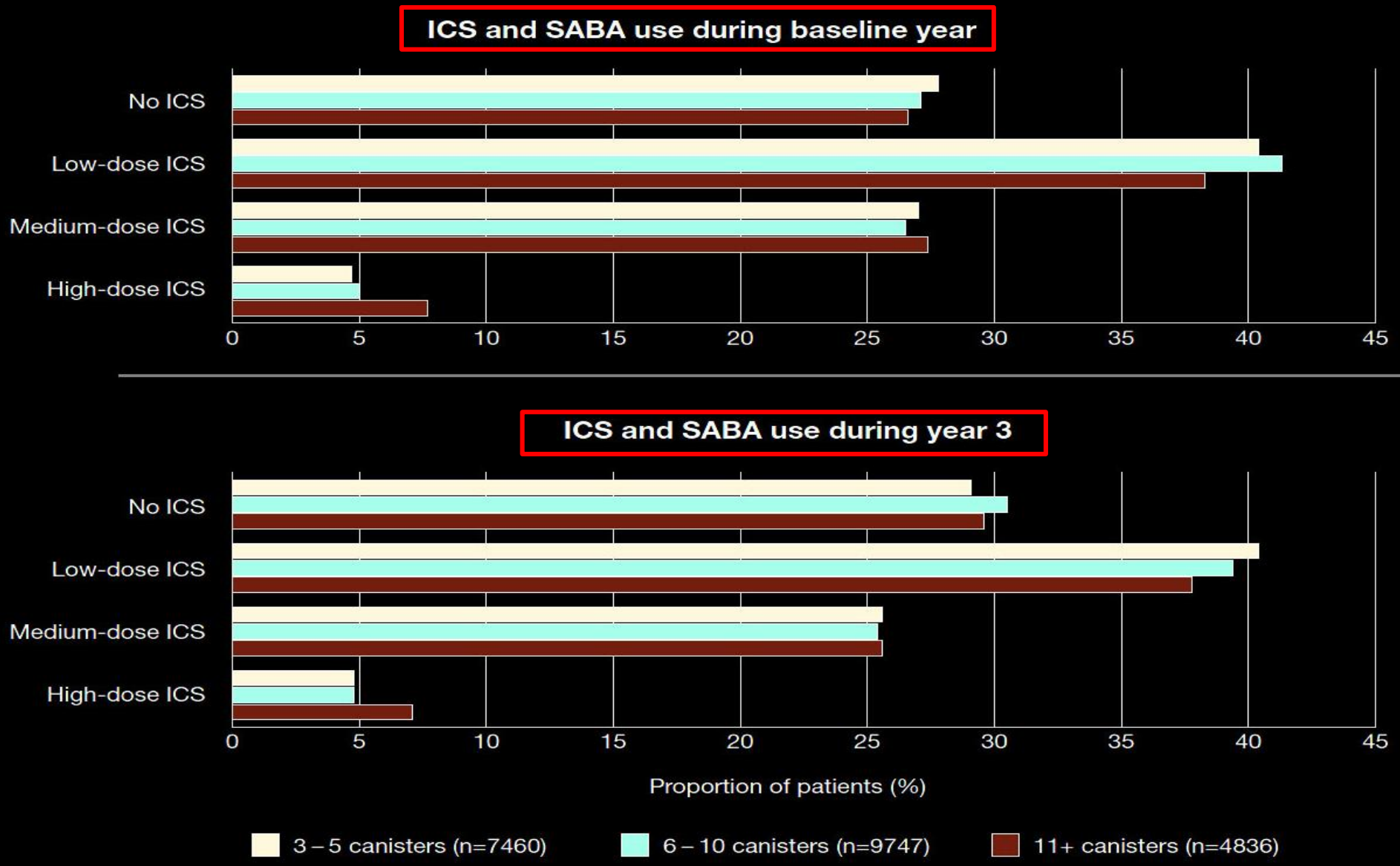


N at risk							
SABA 0 – 2	10905	10192	9727	8990	8180	7586	6993
SABA 3 – 5	3460	3119	2896	2617	2366	2192	2055
SABA 6 – 10	1470	1232	1112	989	901	819	753
SABA 11+	528	399	338	297	261	240	214

Ekstrom M et al. ERSA Congress, 2019, Madrid

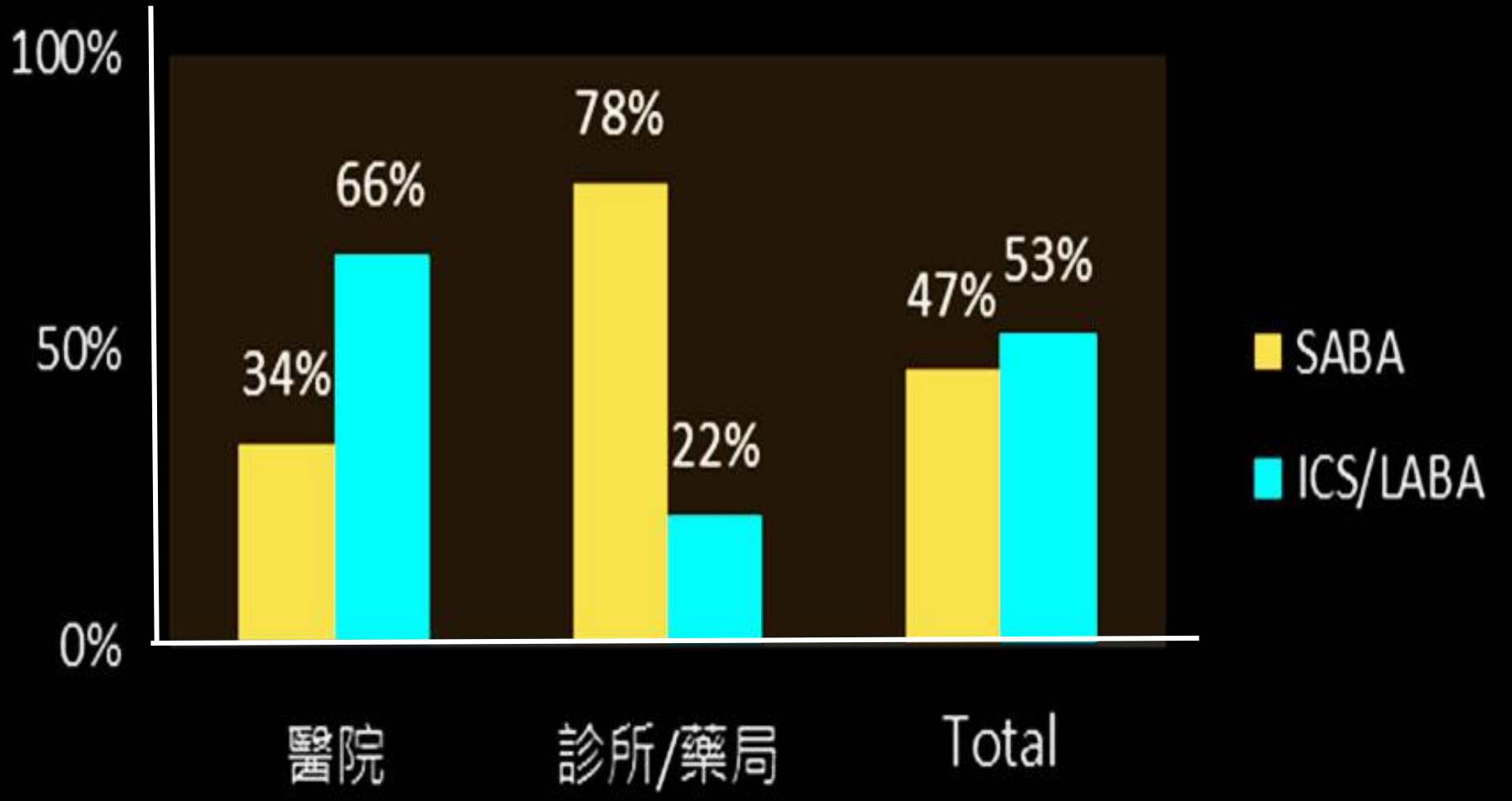
HERA

% of patients on ICS among continuous SABA overuse patients during 3-year follow-up



Ekstrom M et al. ERSA Congress, 2019, Madrid

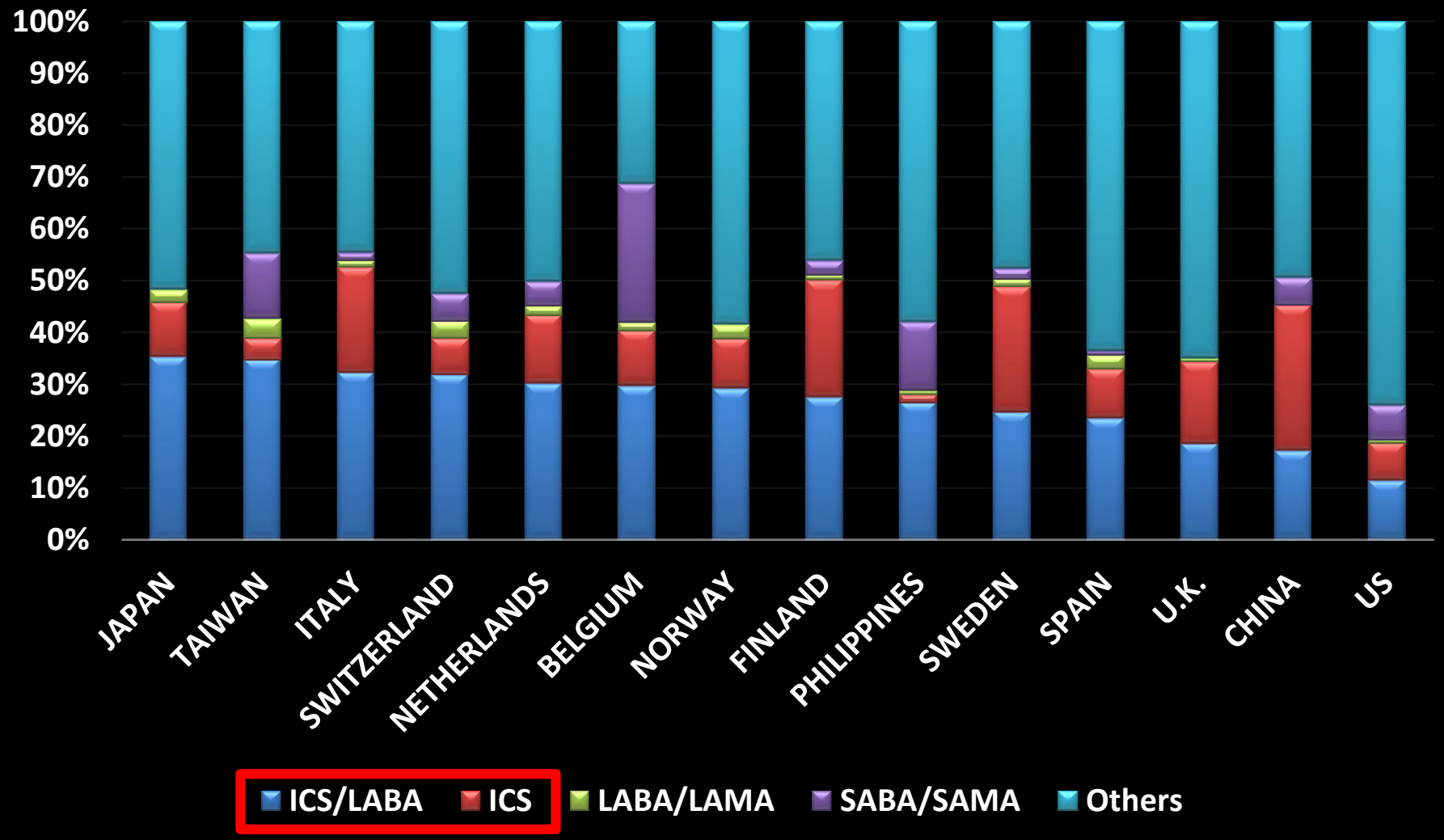
台灣 SABA 與 ICS/LABA 使用現況



- 2018年全台灣SABA銷售量約95萬支
- 台灣SABA vs ICS/LABA (支數) 占比約47%:53%

ZP data.2018

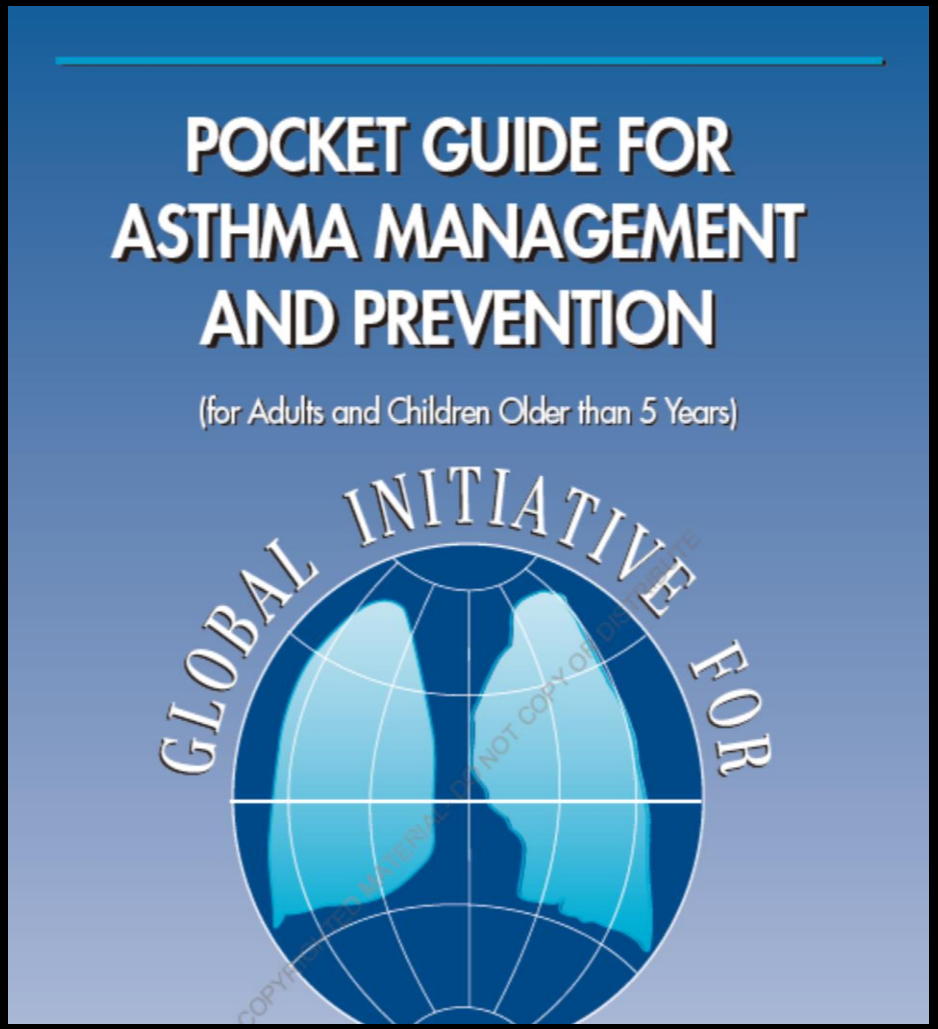
Global inhaler Market



Taiwan: still high SABA/SAMA prescription

DATA SOURCES | IMS MAT AUG 2018 (pharmacy sales, retail & hospital where available). Volume is Counting Units. Data based on GLOBAL AZ Market Definition ETC Market.

GINA 2019 指引更新



POCKET GUIDE FOR GINA 2019 (39 PAGES)

Major changes in the GINA 2019 strategy

- For safety, GINA no longer recommends SABA-only treatment for Step 1
- All adults and adolescents with asthma should receive either symptom-driven (in mild asthma) or daily low dose ICS-containing controller treatment, to reduce their risk of serious exacerbations

GINA 2019

Asthma medication options: GINA 2019

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Preferred controller To prevent exacerbations and control symptoms	As-needed Low dose ICS-formoterol +	Daily low dose ICS or as-needed low dose ICS-formoterol +	Low dose ICS-LABA	Medium dose ICS-LABA	High dose ICS-LABA Refer for phenotypic assessment ± add-on therapy, e.g. tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R
Other controller options	Low dose ICS taken whenever SABA is taken	LTRA, or Low dose ICS taken whenever SABA taken #	Medium dose ICS, or low dose ICS+LTRA	High dose ICS, add-on tiotropium, or add-on LTRA **	Add low dose OCS, but consider side effect
Preferred reliever	As-needed low dose ICS-formoterol +		As-needed low dose ICS-formoterol *		
Other reliever options	As needed SABA				

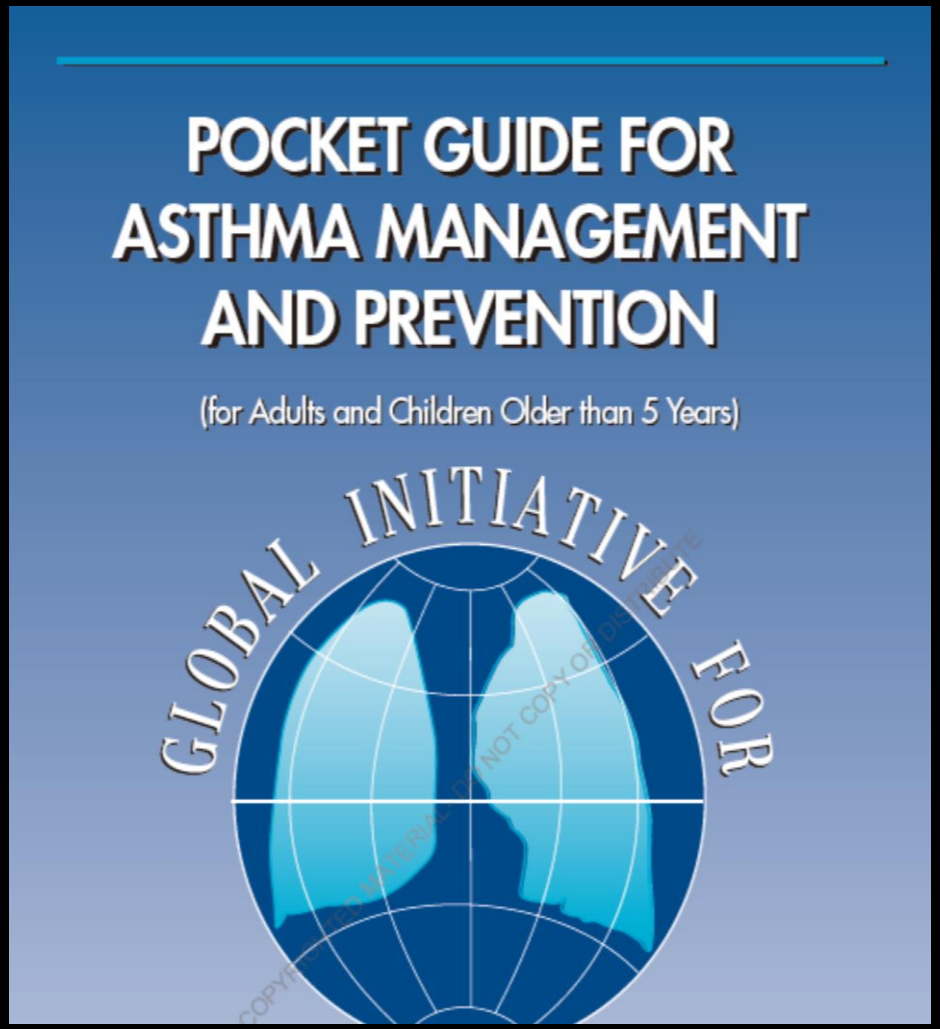
\+ Off-label: Data only with Budesonide-formoterol (Bud-Form)

\# Off-label: separate or combination ICS and SABA inhalers

* Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy.

** Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV_1>70% predicted.

Landmark changes in asthma management



- **The most important change in asthma management in 30 years**

History of Asthma guidelines

1985	Adverse effects and complications of treatment with β-adrenergic agonist drugs (AAAI)
1987	Standards for diagnosis and care of COPD/asthma (ATS)
1989	Australian Asthma handbook
1990	Guideline for the management of asthma in adults (BTS)
1991	NAEPP Expert Panel I Report
1995	Global Initiative for Asthma (GINA)
1995	Japanese Guidelines (Allergy)
1996	Canadian Asthma Consensus
1997	NAEPP Expert Panel II Report (NHLBI)
1997	British Guideline on the Management of Asthma
2007	NAEPP Expert Panel III Report
2011	BTS/SIGN asthma guideline (latest update)
	…

Step 1

	GINA 2018	GINA 2019
Preferred controller to prevent exacerbations and control symptoms		As-needed low dose ICS-formoterol *
Other controller Options	Consider low-dose ICS	Low dose ICS taken whenever SABA is taken +
Preferred reliever	As-needed SABA	As-needed low dose ICS-formoterol *
Other reliever options		As-needed SABA

* Off-label: Data only with Bud-Form

+ Off-label: separate or combination ICS and SABA inhalers

Step 2

	GINA 2018	GINA 2019
Preferred controller	Low dose ICS	Daily low dose ICS or as-needed low dose ICS-formoterol *
Other controller Options	LTRA, or low dose theophylline	LTRA, or Low dose ICS taken whenever SABA taken +
Preferred reliever	As-needed SABA	As-needed low dose ICS-formoterol *
Other reliever options		As-needed SABA

* Off-label: Data only with Bud-Form

+ Off-label: separate or combination ICS and SABA inhalers

ICS use in asthma

- Most patients do not need more than low dose ICS (most benefit is obtained at low doses)
- Can be started with as-needed low dose ICS-form (or low dose ICS whenever SABA is taken) or daily low dose ICS.
- Starting at medium/high dose ICS or low-dose ICS-LABA if on most days the patient has troublesome asthma symptoms; or is waking from asthma once or more a week.
- Consider stepping down after asthma has been well-controlled for 3 months
- However, ICS should not be completely stopped (for ≥ 12 y/o)

GINA 2019

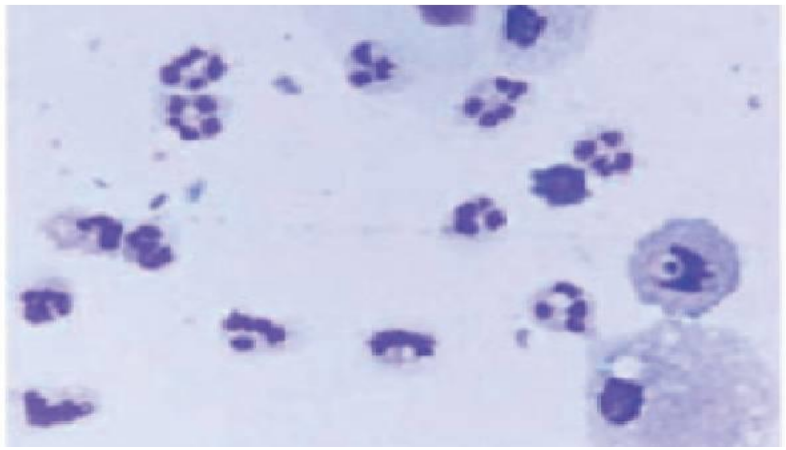
Clinical scenario 2

- 27 y/o F, mild persistent asthma.
- 2019-1-25: ACT 24, PEFR: 380/380, Rx: Symbicort 1 IH bid & prn
- 2019-9-25: ACT 25, PEF: 370/380.
- 醫師: 最近情況怎麼樣？
- 病人: 很好. 我氣喘已經好了. 沒有喘鳴, 已經兩個月沒吸藥.
- 醫師: 那妳有甚麼不舒服嗎？
- 病人: 沒甚麼不舒服, 都不會喘.
- 醫師: 最近日夜溫差較大, 妳早上醒來會不會咳嗽?
- 病人: 只是偶而喉嚨癢

- 醫師: 氣喘通常不會完全緩解或根治, 妳目前屬於輕度氣喘. 請妳有症狀一定要吸藥, 以免長期發炎導致以後進展成為中度或重度氣喘

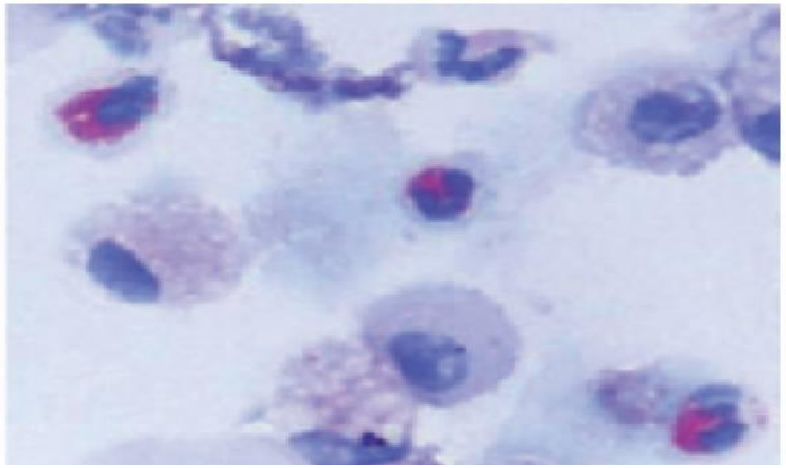
Inflammatory subtypes of asthma

(a)



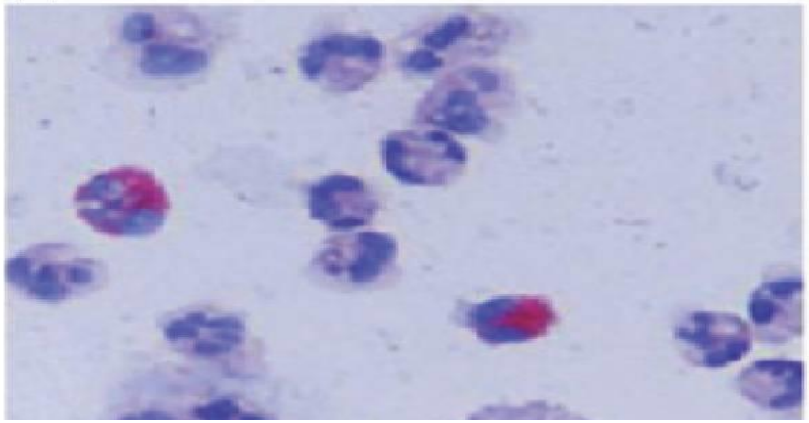
Neutrophilic asthma

(b)



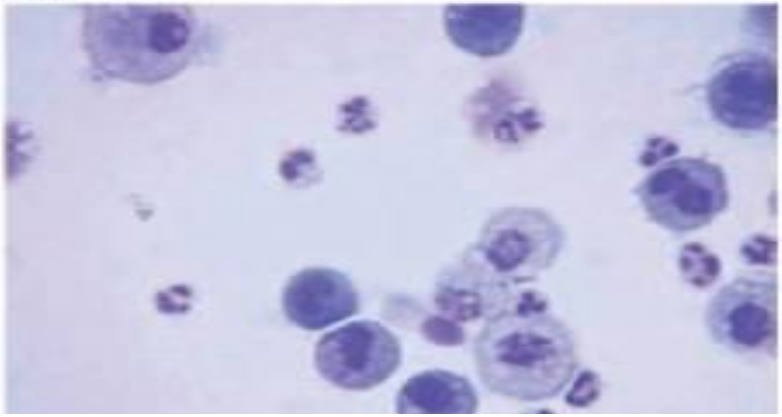
Eosinophilic asthma

(c)



Mixed granulocytic asthma

(d)



Paucigranulocytic asthma

Simpson et al Respirology 2006: 11,54-61

A Large Subgroup of Mild-to-Moderate Asthma Is Persistently Noneosinophilic

Kelly Wong McGrath[1], Nikolina Icitovic[2], Homer A. Boushey[1], Stephen C. Lazarus[1], E. Rand Sutherland[3], Vernon M. Chinchilli[2], and John V. Fahy[4], for the Asthma Clinical Research National Heart, Lung, and Blood Institute

[1]Cardiovascular Research Institute, and [4]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Univer Francisco, San Francisco, California; [2]Public Health Sciences, Penn State Hershey College of Medicine, Hershey, Pennsylvania Medicine, National Jewish Health, Denver, Colorado

- **Sputum eosinophilia (>2%):**

1. **36% in asthmatics not on ICS (n = 350)**
2. **17% in ICS-treated patients (n = 645)**

- **Repeated measures in ICS-treated asthmatics:**

1. **22% Persistent eosinophilia**
2. **31% Intermittent eosinophilia**
3. **47% Persistently noneosinophilic**

Am J Respir Crit Care Med Vol 185, Iss. 6, pp 612–619, Mar 15, 2012

Canada 1997-2012

Transition from mild to moderate/severe asthma

Long-Term Trajectories of Mild Asthma in Adulthood and Risk Factors of Progression

- N = 70,829, 14-45 y/o, newly diagnosed mild asthma, Canada

Only 8% transitioned to moderate or severe asthma over 10 years

Chen W. J Allergy Clin Immunol Pract. 2018 May 7

Canada 1997-2012

Factors affecting the transition from mild to moderate/severe asthma over 10 years

	OR	95% CI	p
Inappropriate SABA use	1.79	1.68-1.90	< 0.001
Older age (per 10-yr increase in age)	1.24	1.22-1.27	< 0.001
Allergic rhinitis	0.95	0.91-1.00	0.063
ICS only	Reference		
ICS/LABA	0.92	0.87-0.97	0.004

Chen W. J Allergy Clin Immunol Pract. 2018 May 7

Step 3

	GINA 2018	GINA 2019
Preferred controller	Low dose ICS/LABA	Low dose ICS-LABA
Other controller Options	Medium/high dose ICS, or low dose ICS + LTRA (or + theophylline)	Medium dose ICS, or low dose ICS + LTRA #
Preferred reliever	As-needed SABA or low dose ICS/formoterol ‡	As-needed low dose ICS-formoterol ‡
Other reliever options		As-needed SABA

‡ Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy. # Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV_1>70%

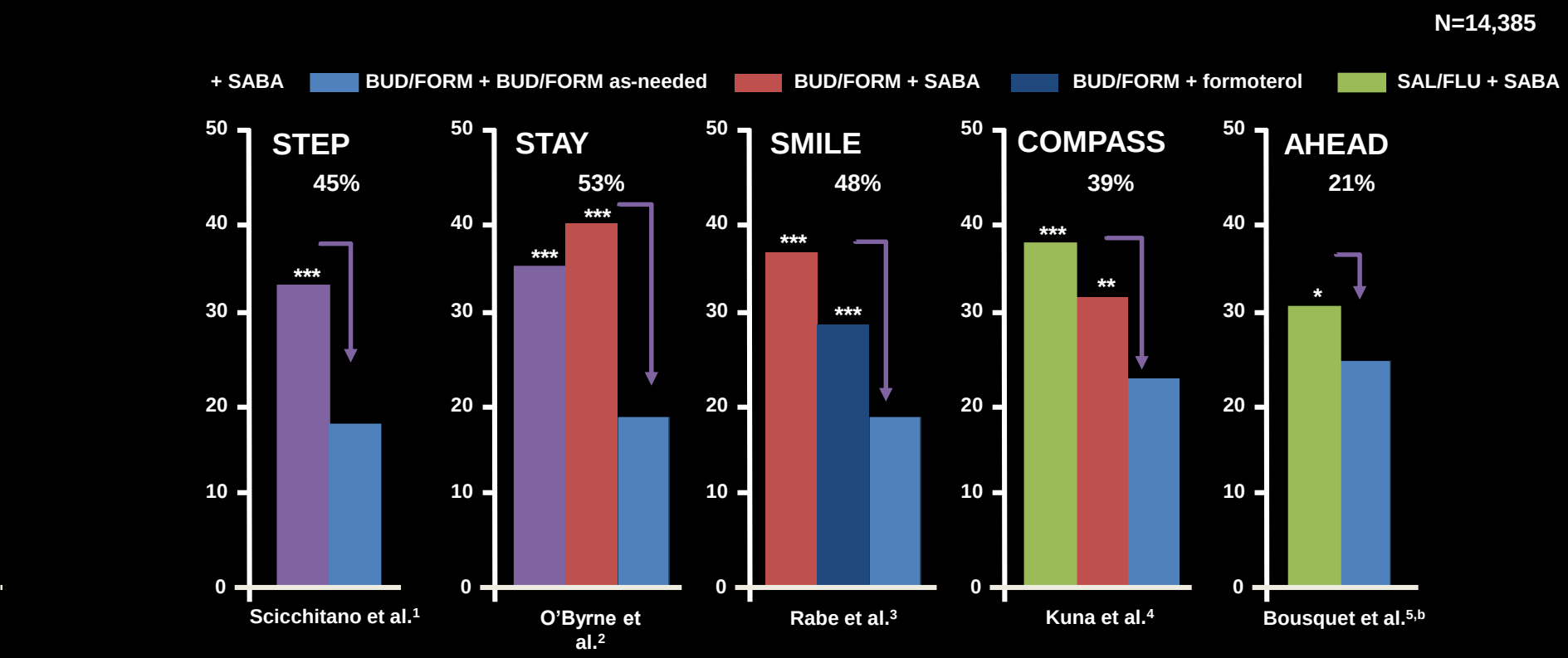
Step 4

	GINA 2018	GINA 2019
Preferred controller	Med/high dose ICS/LABA	Medium dose ICS-LABA
Other controller Options	Add tiotropium, med/high dose ICS + LTRA LTRA (or + theophylline)	High dose ICS, add-on tiotropium, or add-on LTRA. #
Preferred reliever	As-needed SABA or low dose ICS/form ‡	As-needed low dose ICS-form ‡
Other reliever options		As-needed SABA

‡ Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy. # Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV_1>70%

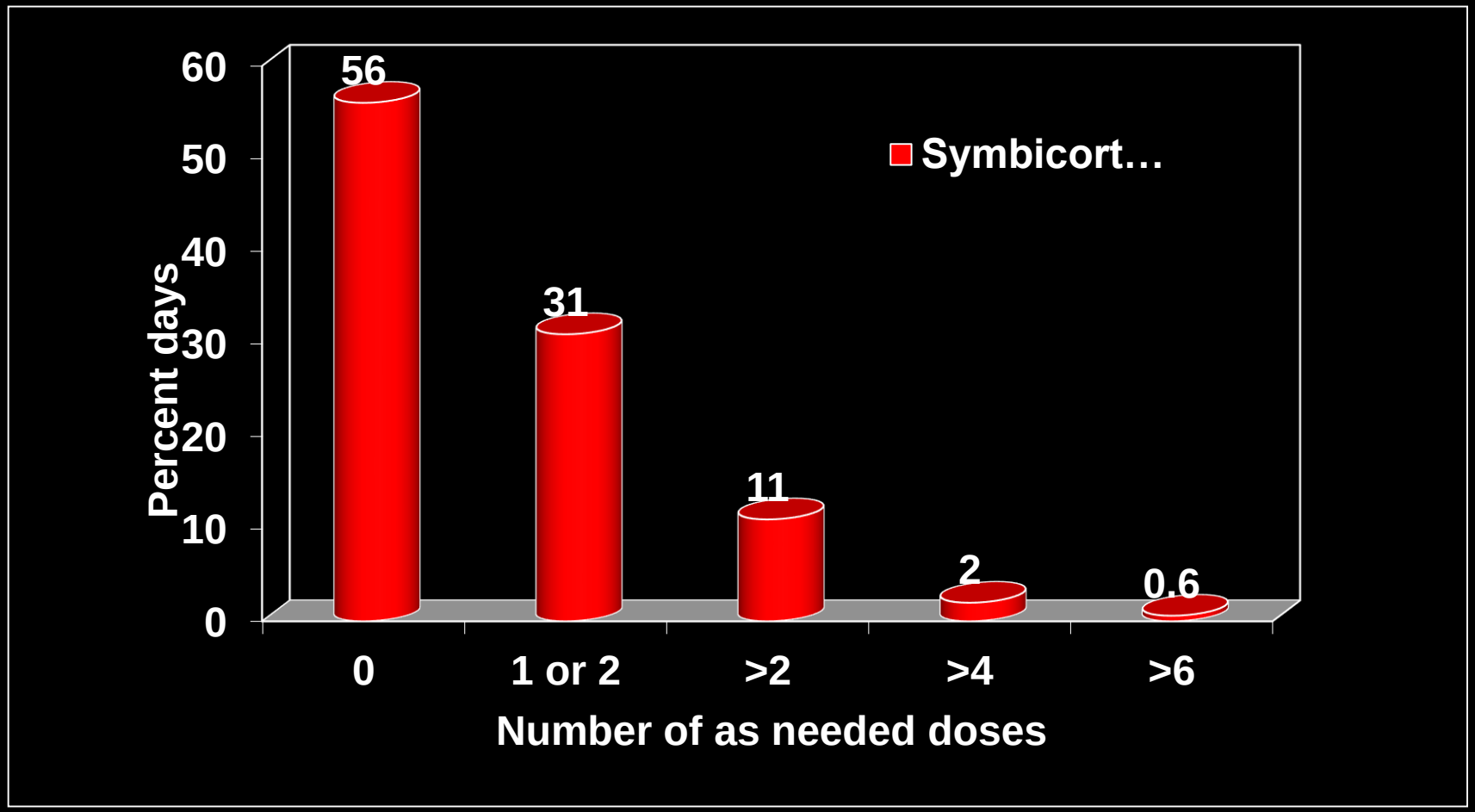
Reduced Rates of Severe Exacerbations With Bud-Form

Anti-inflammatory Reliever + Maintenance in Moderate to Severe Asthma



[a]Reported rates of severe exacerbation were those requiring medical intervention (ie, hospitalization/ED treatment due to worsening asthma, or the need for systemic CS for asthma); [b]This study did not achieve its primary endpoint (time to first severe exacerbation). *p=0.039 vs. BUD/FORM maintenance and reliever; **p=0.0048 vs. BUD/FORM maintenance and reliever; ***p<0.001 vs. BUD/FORM maintenance and reliever. 1. Scicchitano R et al. *Curr Med Res Opin.* 2004;20:1403-1418; 2. O'Byrne PM et al. *Am J Respir Crit Care Med.* 2005;171:129-136; 3. Rabe KF et al. *Lancet.* 2006;368:744-753; 4. Kuna P et al. *Int J Clin Pract.* 2007;61:725-736; 5. Bousquet J et al. *Respir Med.* 2007;101:2437-2446.

As needed use of Bud-Form in clinical trials



Rabe KF, et al. Chest 2006;
Scicchitano R, et al. Curr Med Res Opin 2004
Kuna P, et al. Int J Clin Pract 2007

O'Byrne PM, et al. Am J Respir Crit Care Med 2005;
Rabe KF, et al. Lancet 2006

Cochrane Rev

ICS-Formotero vs. ICS alone for asthma: Death and serious adverse events

- 42 studies, n = 35,751

Death:

- OR: 1.25 (0.61 - 2.56, moderate-certainty evidence)

Non-fatal serious adverse events

- OR : 1.00 (0.87 to 1.16, high-certainty evidence).

Asthma-related serious adverse events

- OR: 0.86 (0.64 to 1.14, moderate-certainty evidence)

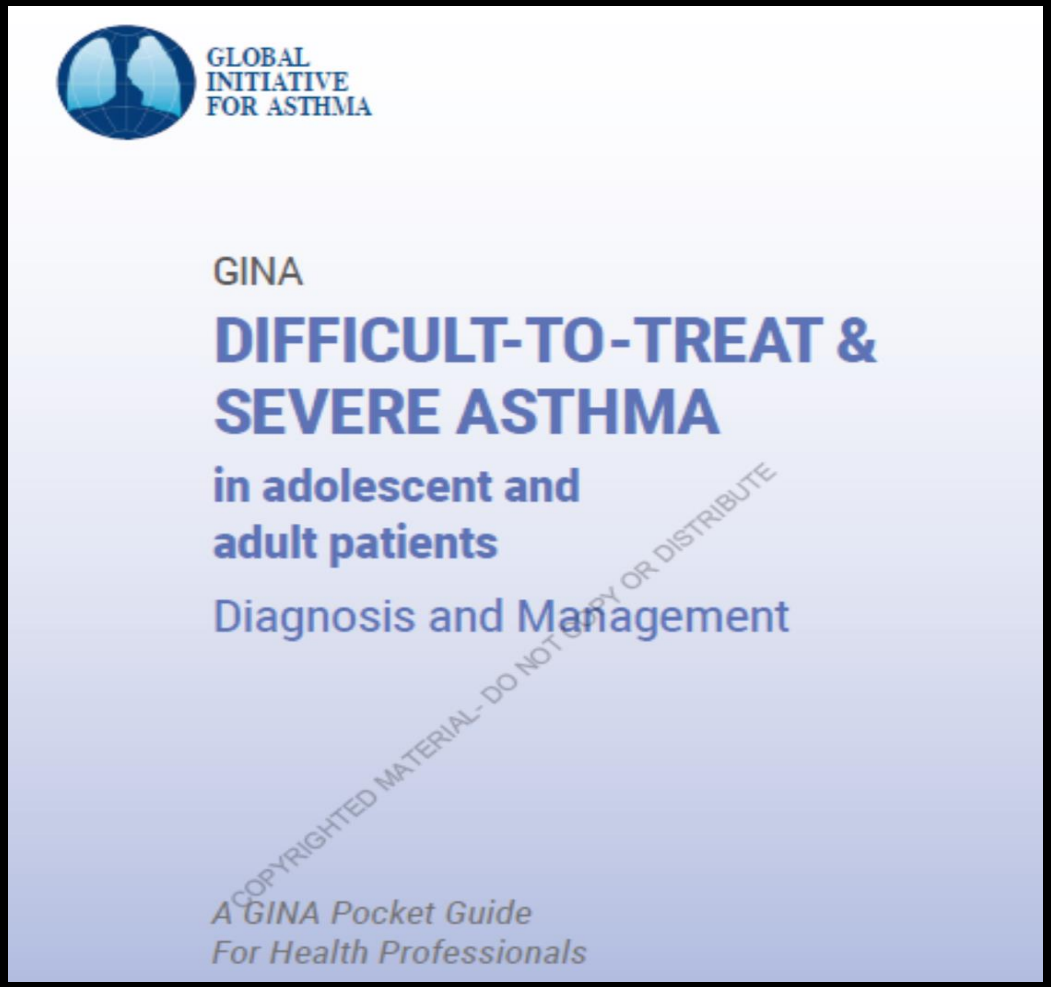
CONCLUSIONS:

- We did not find a difference in the risk of death (all-cause or asthma-related) in adults taking ICS + formoterol vs. ICS alone

Janjua S, Cochrane Database Syst Rev. 2019 Sep 25;9:CD006924

2018-11-22: A GINA pocket guide for health professionals

Difficult-to-treat and severe asthma



(adolescent and adults)
Diagnosis and management

Poor adherence is common in omalizumab users

Original Article

Trends in Omalizumab Utilization for Asthma: Evidence of Suboptimal Patient Selection

Molly M. Jeffery, PhD[a,b], Nilay D. Shah, PhD[a,b], Pinar Karaca-Mandic, PhD[c], Joseph S. Ross, MD, MHS[d,e,f], and Matthew A. Rank, MD[b,g] *Rochester and Minneapolis, Minn; New Haven, Conn; and Scottsdale, Ariz*

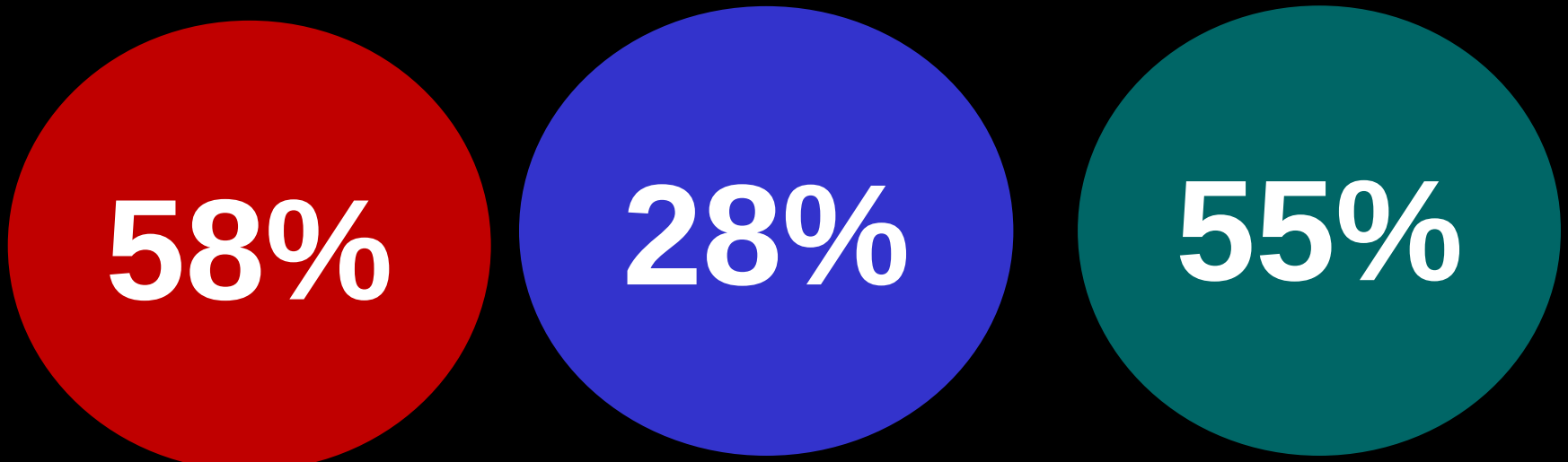
- USA, 2003 – 2015, 7,658 prevalent and 3,399 incident omalizumab users
- Medication possession ratio (MPR) to ICSs and/or ICS-LABA
- 12 months before omalizumab initiation:

1. 72.5% had low adherence (MPR ≤ 0.75)
2. 48.6% had very low adherence (MPR ≤ 0.5)

J Allergy Clin Immunol Pract 2017

REALISE Asia

Inhaler Technique Checks by Healthcare Professionals (HCPs)



Check their patients inhaler technique

Think that their patients are using inhalers incorrectly

Always/mostly check patients' inhaler technique in follow-up consultations.

Chisholm A. NPJ Prim Care Respir Med. 2017 Jan 5;27:16089

Difficult-to-treat asthma

- Uncontrolled despite:

1. Step 4 or 5 treatment, or
2. Requiring such treatment to maintain good symptom control and reduce the risk of exacerbations.

- It may come with :

1. Incorrect inhaler technique
2. Poor adherence
3. Smoking
4. Comorbidities
5. Incorrect diagnosis

Severe asthm

- A subset of difficult-to-treat asthma
- Uncontrolled despite :

1. Adherence with maximal optimized therapy and
2. Treatment of contributory factors, or
3. Worsens when high dose treatment is decreased.

- It is not severe asthma if it markedly improves when inhaler technique and adherence are addressed.

GINA 2019

Step 5

	GINA 2018	GINA 2019
Preferred controller to prevent exacerbations and control symptoms	Refer for add-on treatment, e.g.tiotropium, anti-IgE, anti-IL5/5R	High dose ICS-LABA Refer for phenotypic assessment ± add-on therapy, e.g. tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R
Other controller Options	Add low dose OCS	Add low dose OCS, but consider side effect
Preferred reliever	As-needed SABA or low dose ICS/formoterol ‡	As-needed low dose ICS-formoterol ‡
Other reliever options		As-needed SABA

‡ Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy.

2019

GINA recommendations for asthma

	Step 1	Step 2	Step 3	Step 4	Step 5
Preferred controller	As-needed Low dose ICS-formoterol	Daily low dose ICS or as-needed low dose ICS-formoterol	Low dose ICS-LABA	Medium dose ICS-LABA	High dose ICS-LABA Refer for phenotypic assessment add-on therapy, e.g. tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R
Other controller Options	Low dose ICS taken whenever SABA is taken	LTRA, or Low dose ICS taken whenever SABA taken	Medium dose ICS, or low dose ICS+LTRA	High dose ICS, add-on tiotropium, or LTRA	Add low dose OCS, but consider side effect
Preferred reliever	As-needed low dose ICS-form				
Other reliever options	As-needed SABA				

GINA 2019 recommendations about reliever medications in Steps 3-5

We have become aware that the GINA 2019 recommendation for 'Preferred reliever' i Steps 3-5 is sometimes being misinterpreted. Please note the following important information.

In the GINA 2019 treatment figure for adults and adolescents (Box 3-5A), Steps 3-5 show the medication options for patients with moderate to severe asthma in whom modifiable causes of symptoms or exacerbations have been addressed. In these patients, low-dose ICS-formoterol is the preferred reliever only for patients who are prescribed maintenance and reliever therapy with ICS-formoterol.

GINA does not recommend use of ICS-formoterol as the reliever for patients taking combination ICS-LABA medications with a different LABA. For these patients, their as-needed reliever inhaler should be a short-acting b2-agonist (SABA).

https://ginasthma.org/reports/

Preferred reliever in steps 3-5

- **Steps 3-5:**

1. **Low-dose ICS-formoterol is the preferred reliever only if patients are prescribed maintenance and reliever therapy with ICS-formoterol**

2. **GINA does not recommend use of ICS-formoterol as the reliever for patients taking ICS-LABA mediations with a different LABA**

https://ginasthma.org/reports/

GINA 2019

Asthma medication options

Adjust treatment up and down for individual needs

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
					High dose ICS-LABA
Preferred controller To prevent exacerbations and control symptoms	As-needed Low dose ICS-formoterol +	Daily low dose ICS or as-needed low dose ICS-formoterol +	Low dose ICS-LABA	Medium dose ICS-LABA	Refer for phenotypic assessment ± add-on therapy, e.g. tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R
Other controller options	Low dose ICS taken whenever SABA is taken	LTRA, or Low dose ICS taken whenever SABA taken #	Medium dose ICS, or low dose ICS+LTRA	High dose ICS, add-on tiotropium, or add-on LTRA **	Add low dose OCS, but consider side effect
Preferred reliever	As-needed low dose ICS-formoterol +			As-needed low dose ICS-formoterol for patients prescribed maintenance and reliever therapy ‡	
Other reliever options	As needed SABA				

+ Off-label: Data only with Budesonide-formoterol (Bud-Form)

Off-label: separate or combination ICS and SABA inhalers

* Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy.

** Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV_1>70% predicted.

BUD-FORM has been approved for all severities of asthma in these countries :

1. Australia
2. Brazil
3. Canada
4. Chile
5. Haiti
6. New Zealand
7. Russia
8. Singapore
9. Sint Maarten
10. South Korea

Thank You !