

Behind the scene: How simplified regimen help asthma patients relieve their symptoms and reduce reliever use



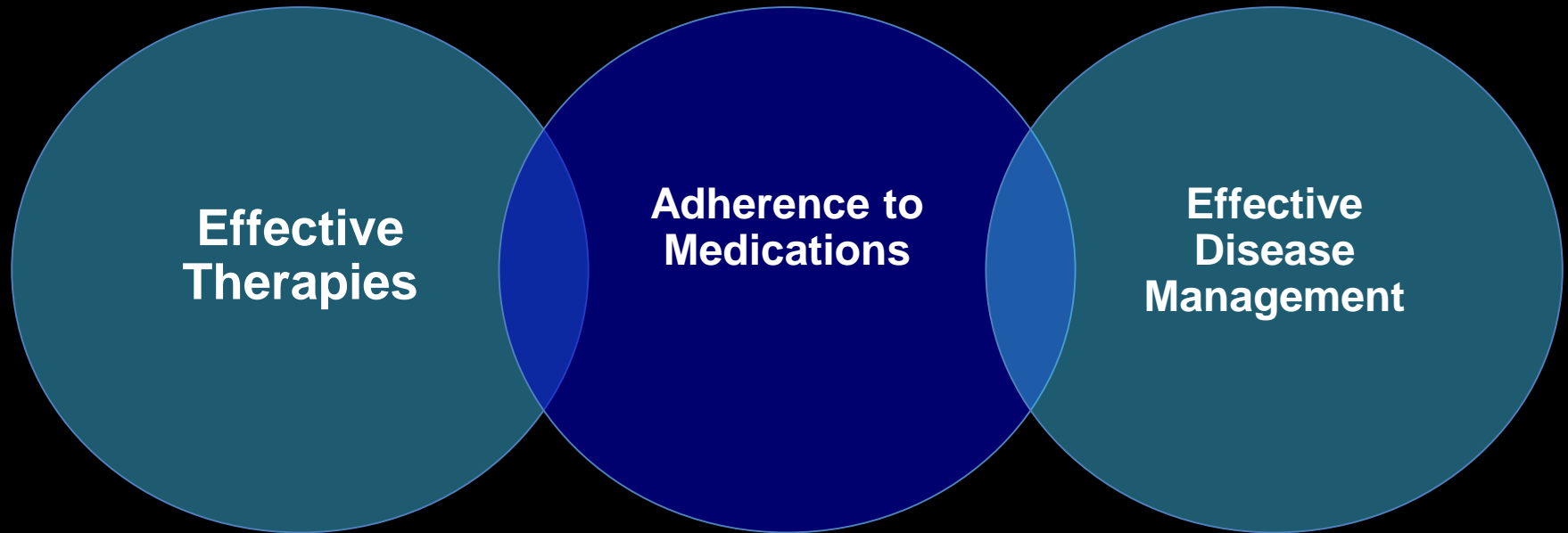
郭炳宏

臺大醫院內科部

Disclaimer

- **This event is sponsored by GSK, in the interest of advancing the scientific knowledge of healthcare professionals.**
- **GSK does not approve of or recommend the use of medicines in any way other than that stated in the approved package inserts.**
- **For full prescribing information, refer to the package inserts approved by TFDA**

Adherence: Key to Therapeutic Success



“Drugs don’t work in patients who do not take them.”

C. Everett Koop, former US Surgeon General

Non-adherence

- **Non-adherence:** described when a patient misses his dose more than 30% of the days in a month.

Indian J Psychol Med. 2012 Apr-Jun; 34(2): 107–109.



Non-Adherence: Not A New Issue !

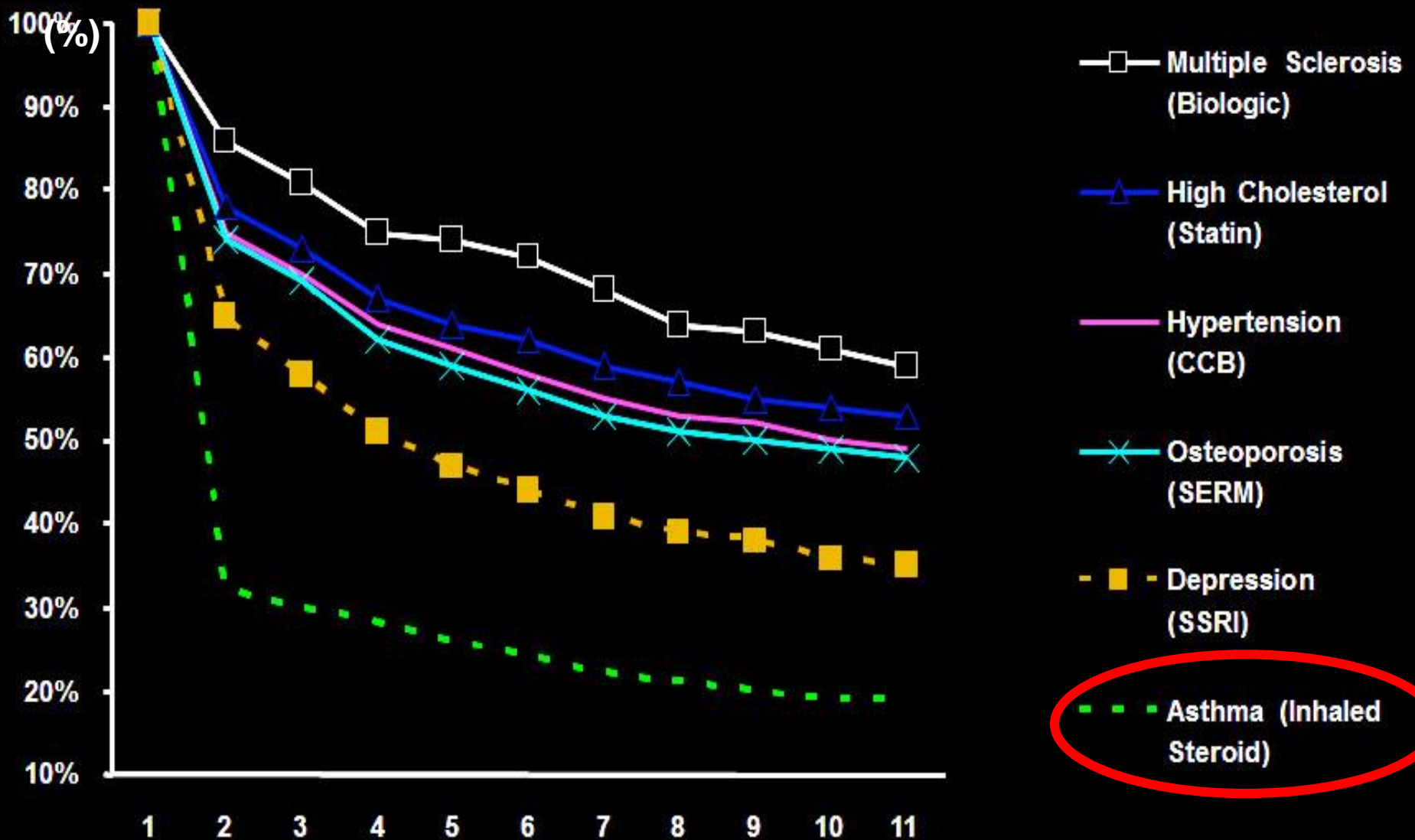
“ Physicians should keep aware of the fact that patients often lie when they state that they have taken certain medicines ”

-

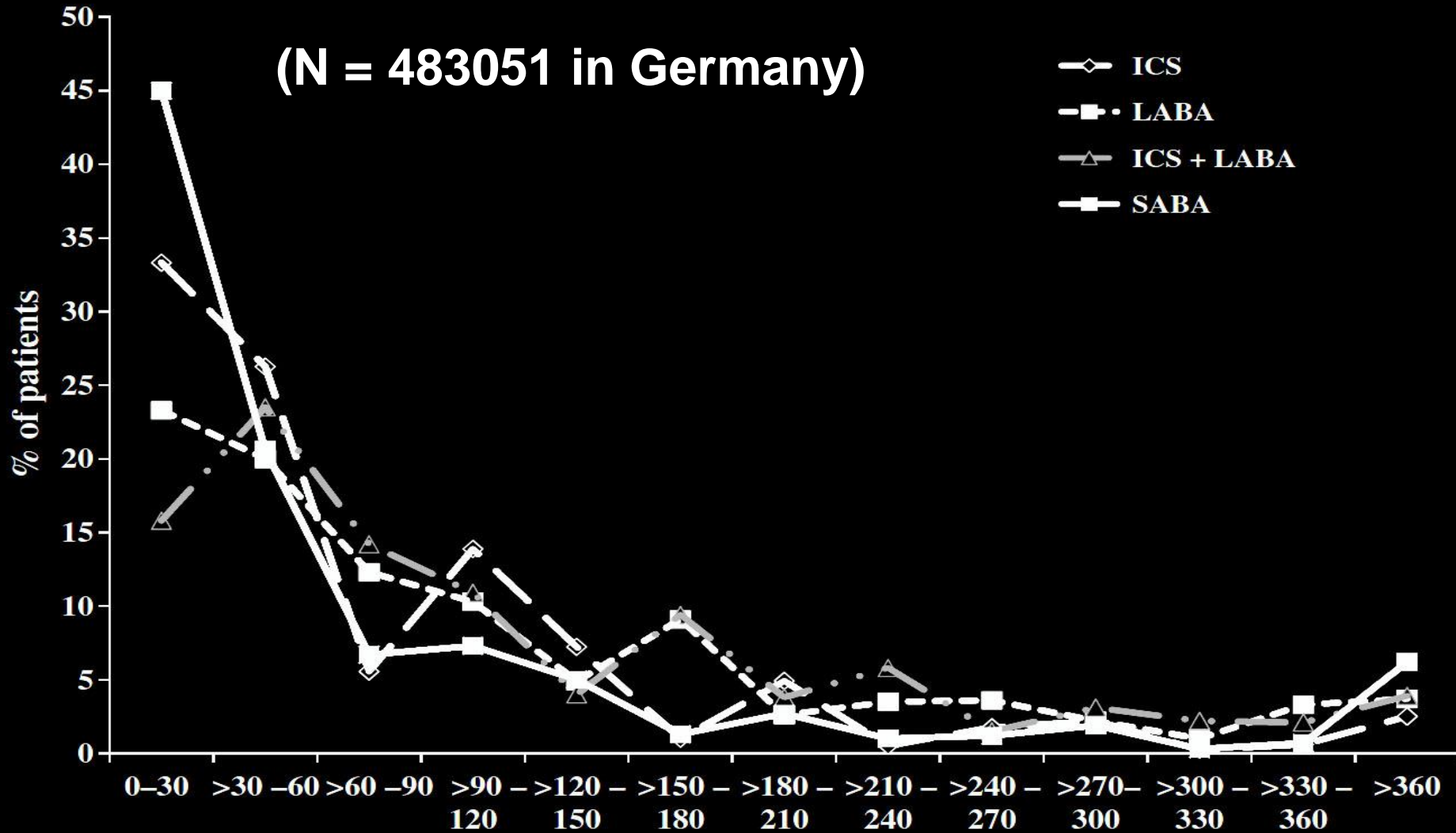
Hippocrates



Patient persistence on medications



% of patients receiving the indicated asthma inhalers over 1 year



Attitudes, symptoms and adherence

91%

were confident in
managing their asthma

43%

used rescue medication \geq
3 times in past 7 days^c

24%

Needed A&E treatment
for asthma in previous
12 months^d

48%

take their ICS
every day

44%

Required oral steroids
for asthma in previous
12 months^e

Base: all respondents from the country-specific analysis, N = 7457; A&E, accident and emergency

^aQ: Which of the following most closely describes your level of confidence in managing your asthma? A: very/fairly confident (combined)

^bQ: Which statement best describes how you take your regular asthma treatment?

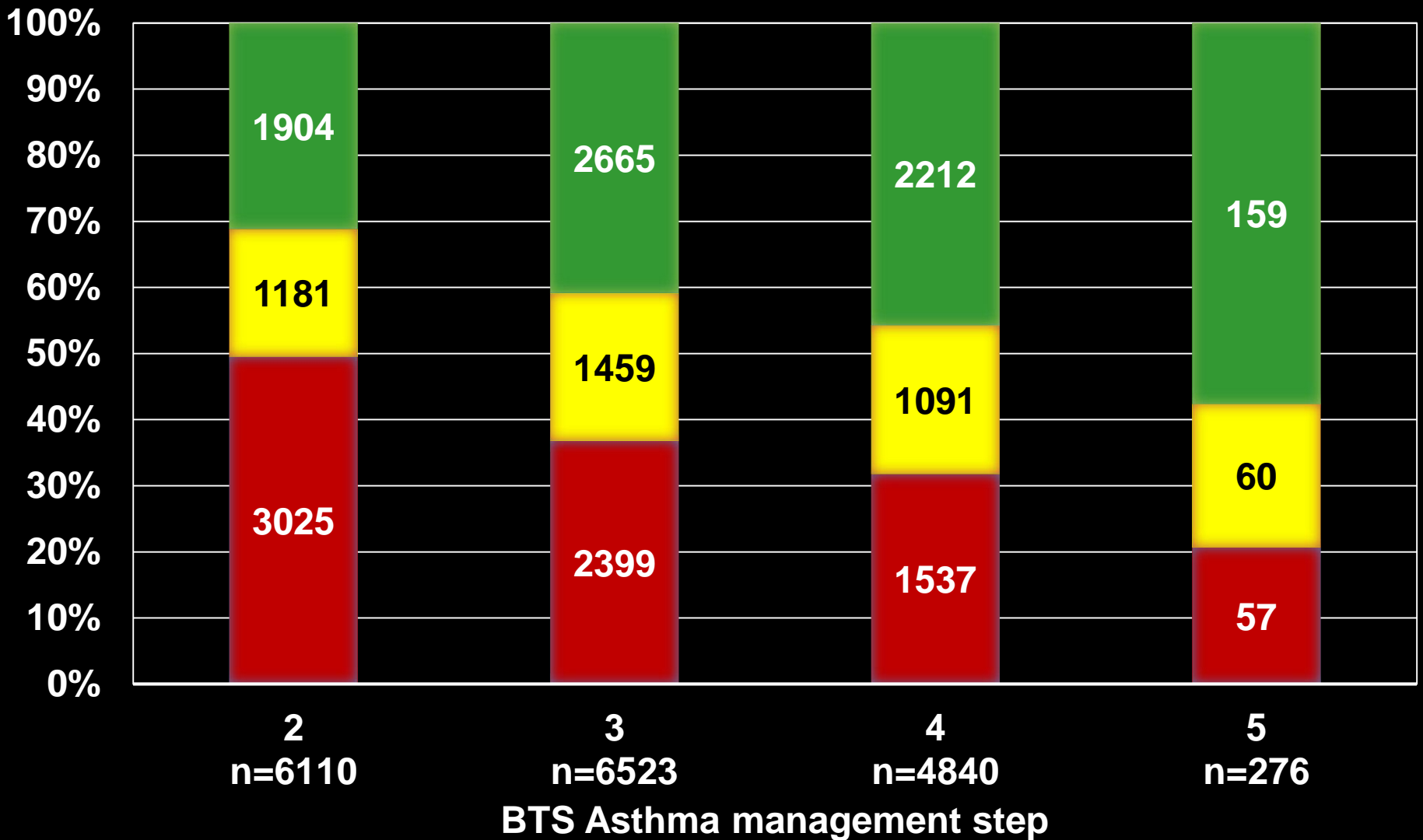
^cQ: Thinking about the last week...how many times have you used your reliever inhaler?

^dQ: How many times have you been treated in Accident and Emergency or the hospital ED for your asthma in the past 12 months?

^eQ: How many times have you needed a course of steroid tablets for worsening asthma? (In the last 12 months...); answers combined for once or more

Level of ICS Adherence in Asthma

Adherence ■ <50% ■ 50-75% ■ >75%



ICS Adherence vs. Asthma Exacerbations in Moderate-to-Severe Asthma

EOS count > 400

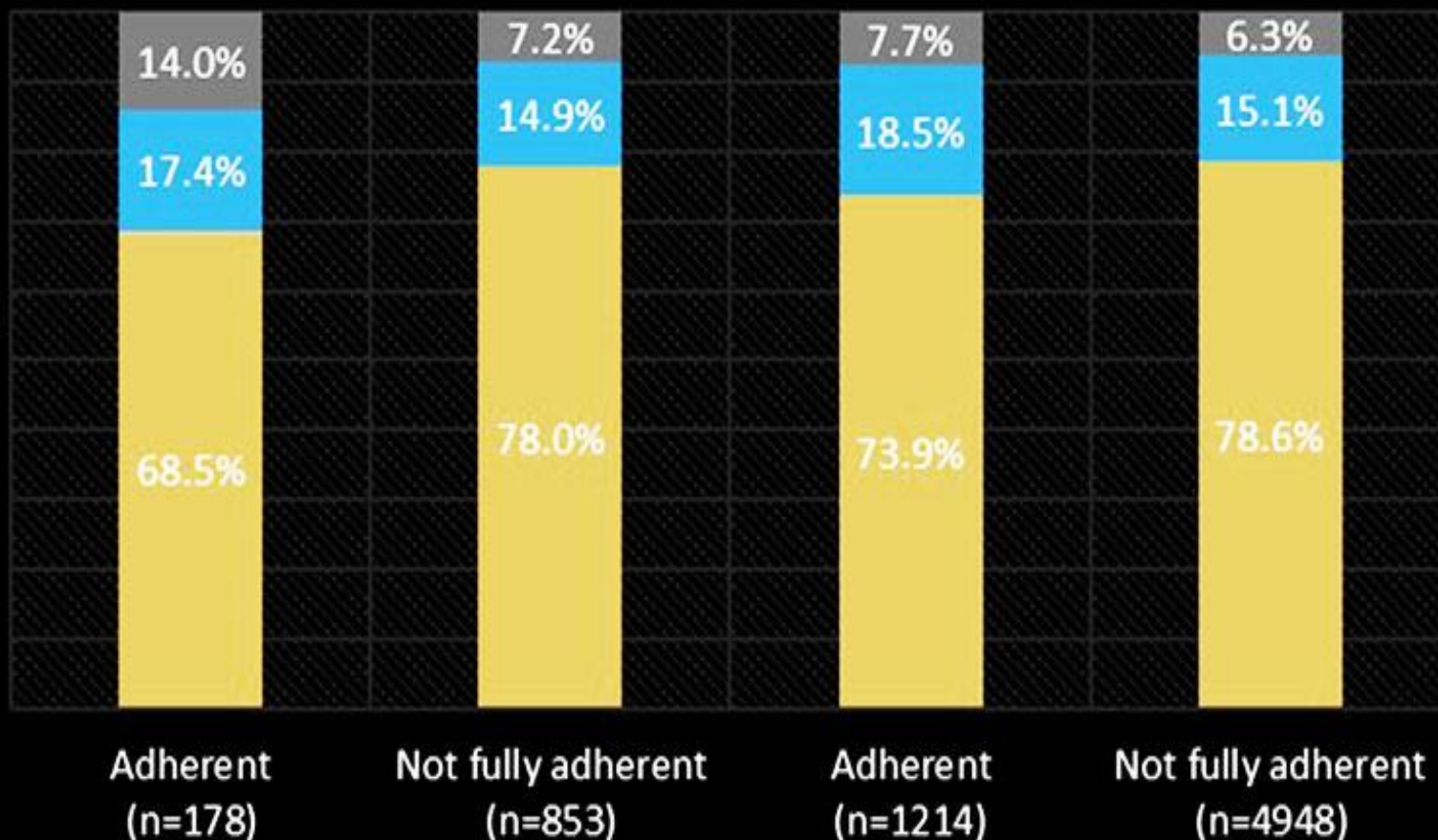
EOS count ≤ 400

$p=0.193^{\dagger}$; $p=0.003^{\ddagger}$

$p=0.001^{\dagger}$; $p=0.080^{\ddagger}$

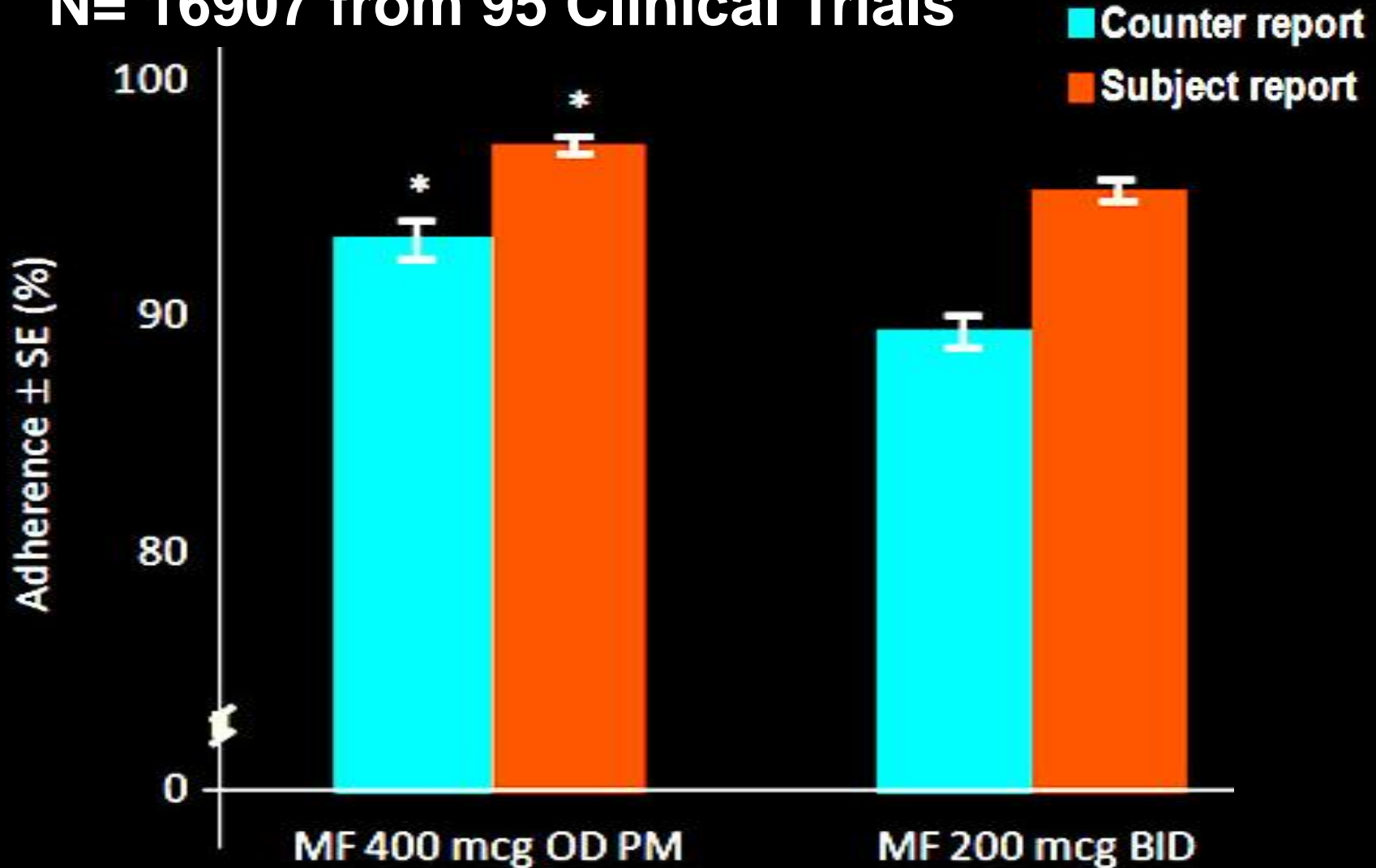
Exacerbation

■ 2+
■ 1
■ 0



Once-Daily Therapy → Better Adherence

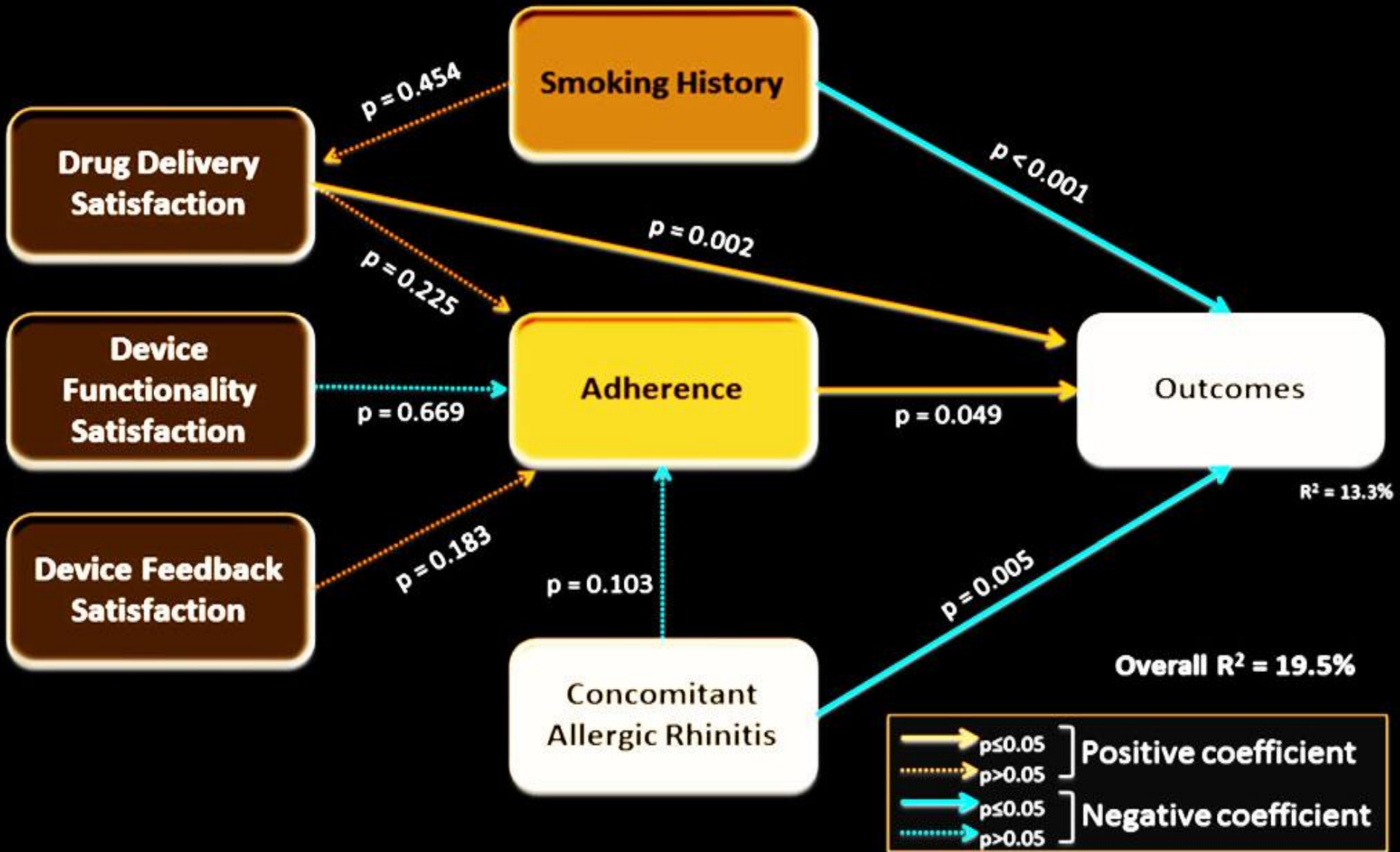
N= 16907 from 95 Clinical Trials



Price D, et al. BMC Pulm Med 2010;10:1

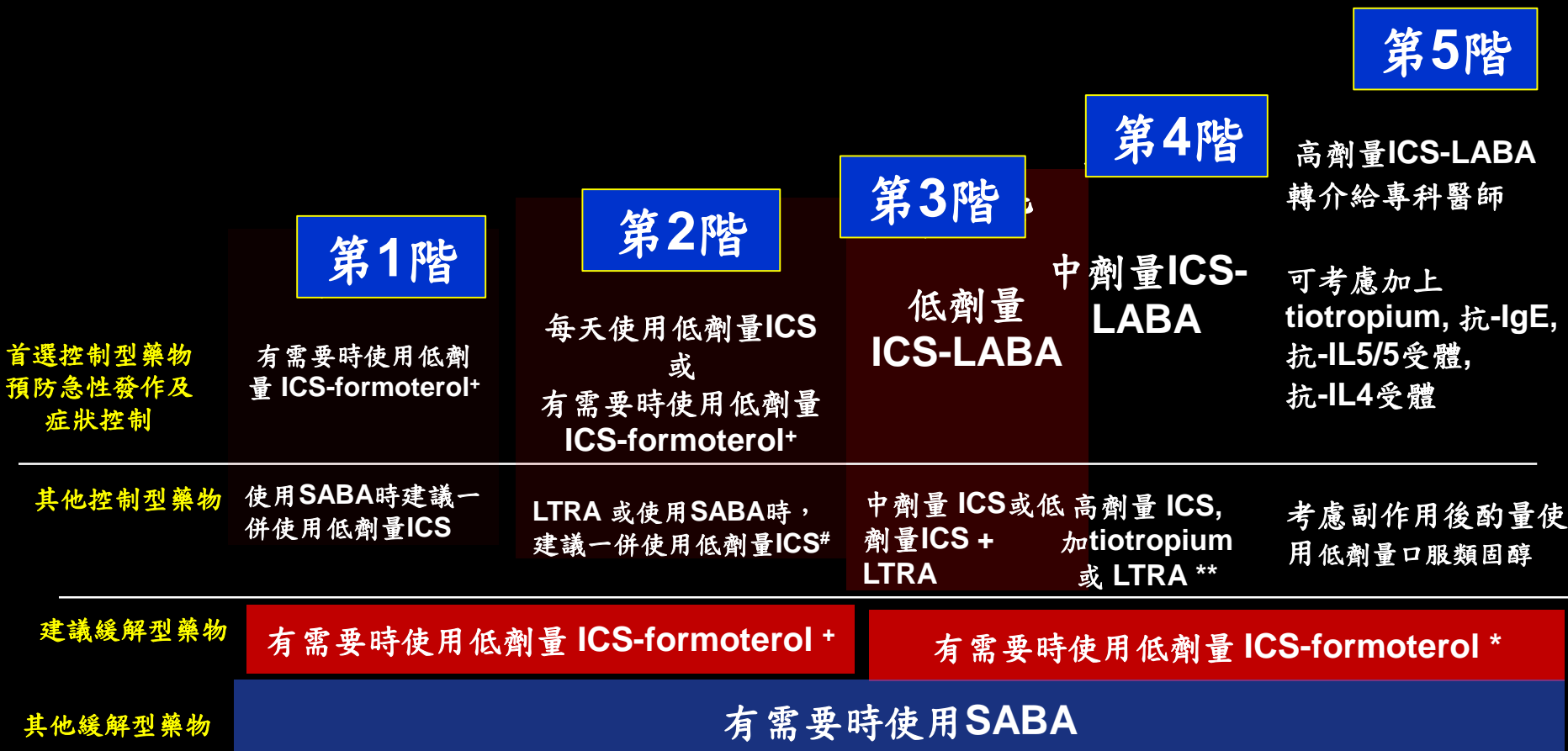
Blaschke TF, et al. Annu Rev Pharmacol Toxicol 2012;52:275-301

Inhaler Satisfaction Improves Asthma outcomes





GINA 2019 氣喘治療指引



- * 當以BUD/form或BDP/form進行維持及緩解療法時，建議使用低劑量的ICS-form作為緩解藥物。
- ** 同時具過敏性鼻炎且FEV₁>70%預測值時，可考慮加上HDM SLIT。

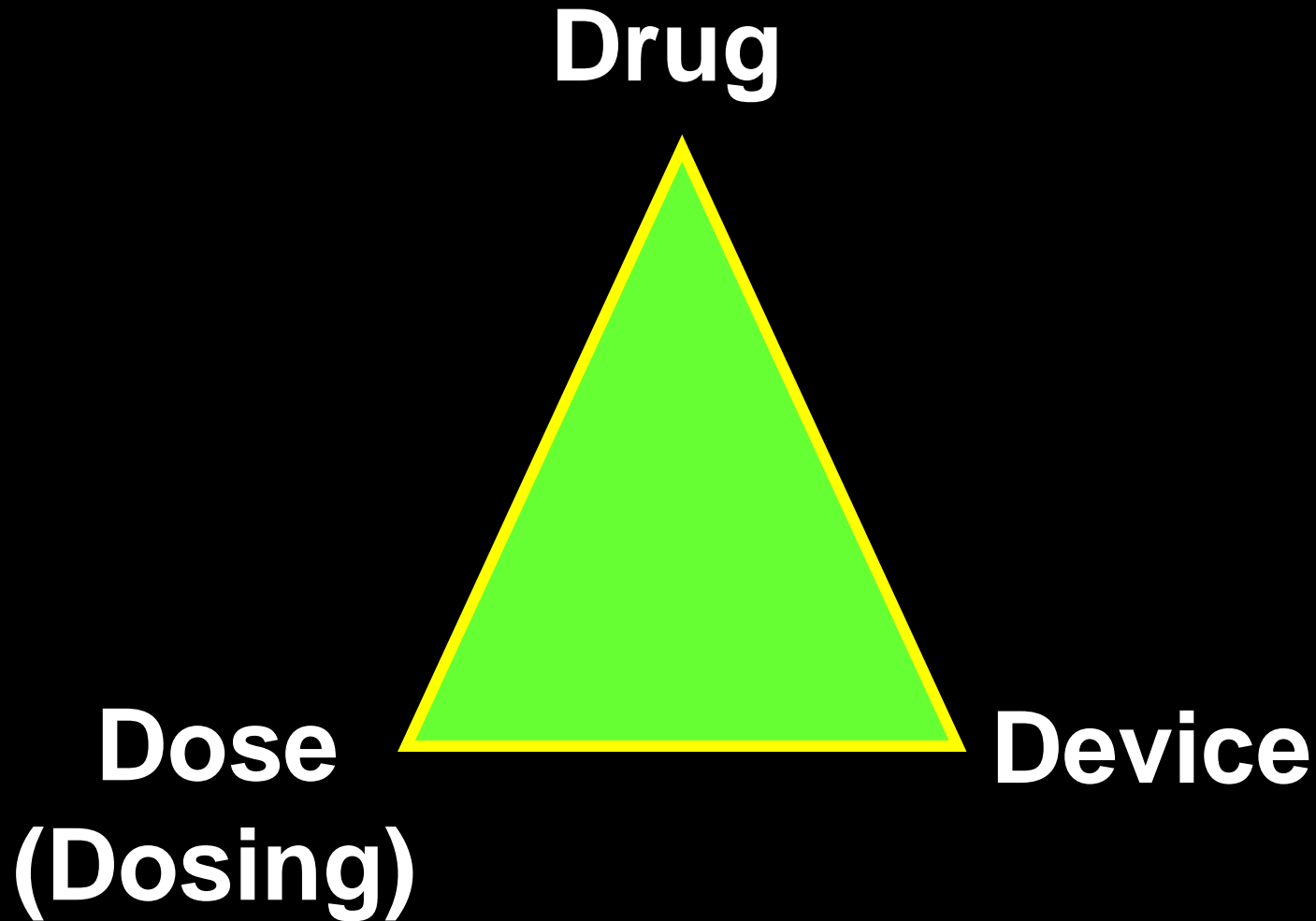
+ 尚未取得適應症: 目前僅 Budesonide-formoterol (Bud-Form)有證據支持

尚未取得適應症: 分開或者複方 ICS/SABA 吸入器

ICS/LABA inhalers in Taiwan: Which is most appropriate for your patients ?



Three “D”’s in inhaler therapy



Drug

- **FF/VI**



商品名: Relvar Ellipta

學名: Fluticasone furoate + Vilanterol

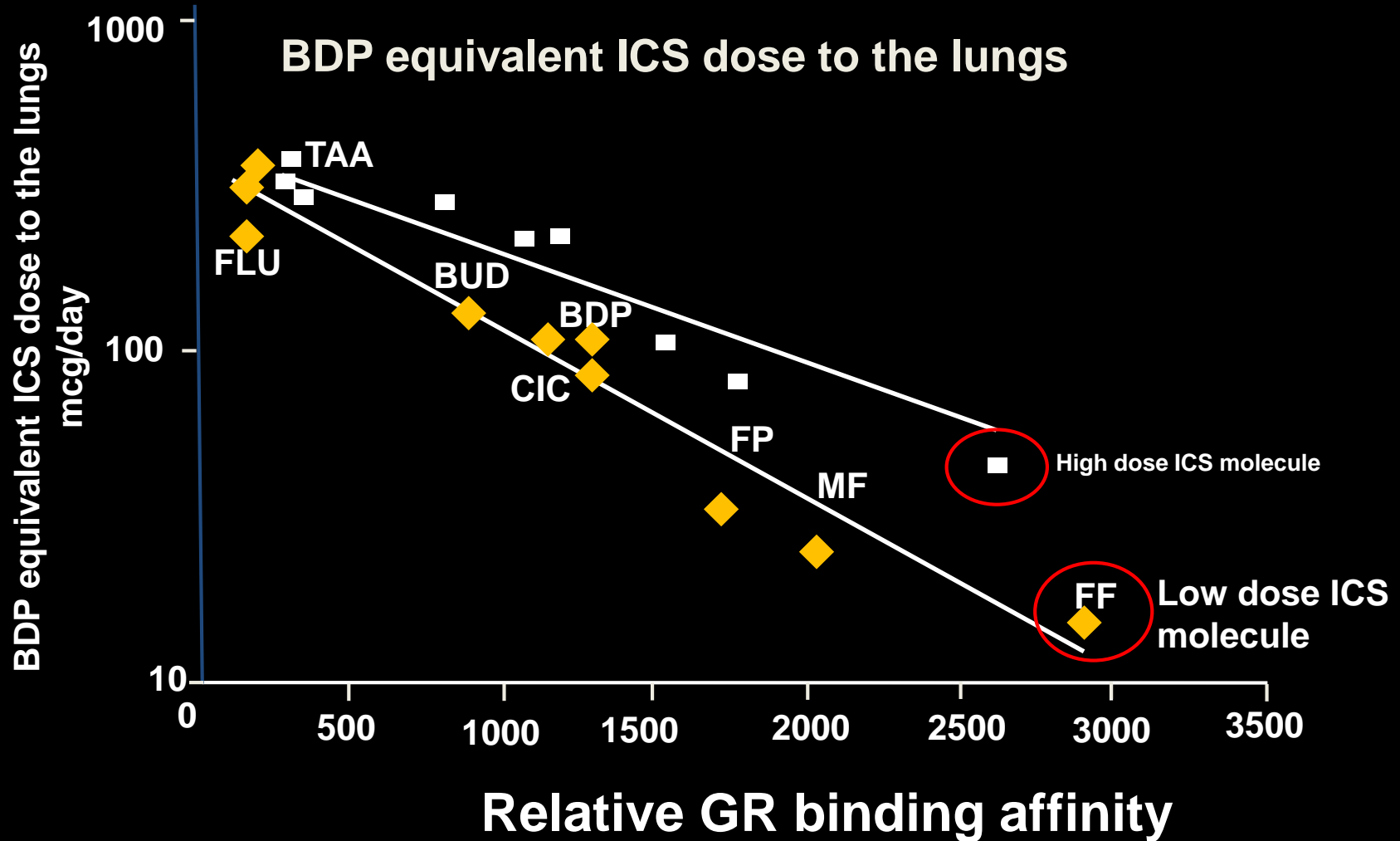
中文名: 潤娃 易利達乾粉吸入器

劑量: 100/25, 200/25 μg /劑 (92/22, 184/22 μg /劑)

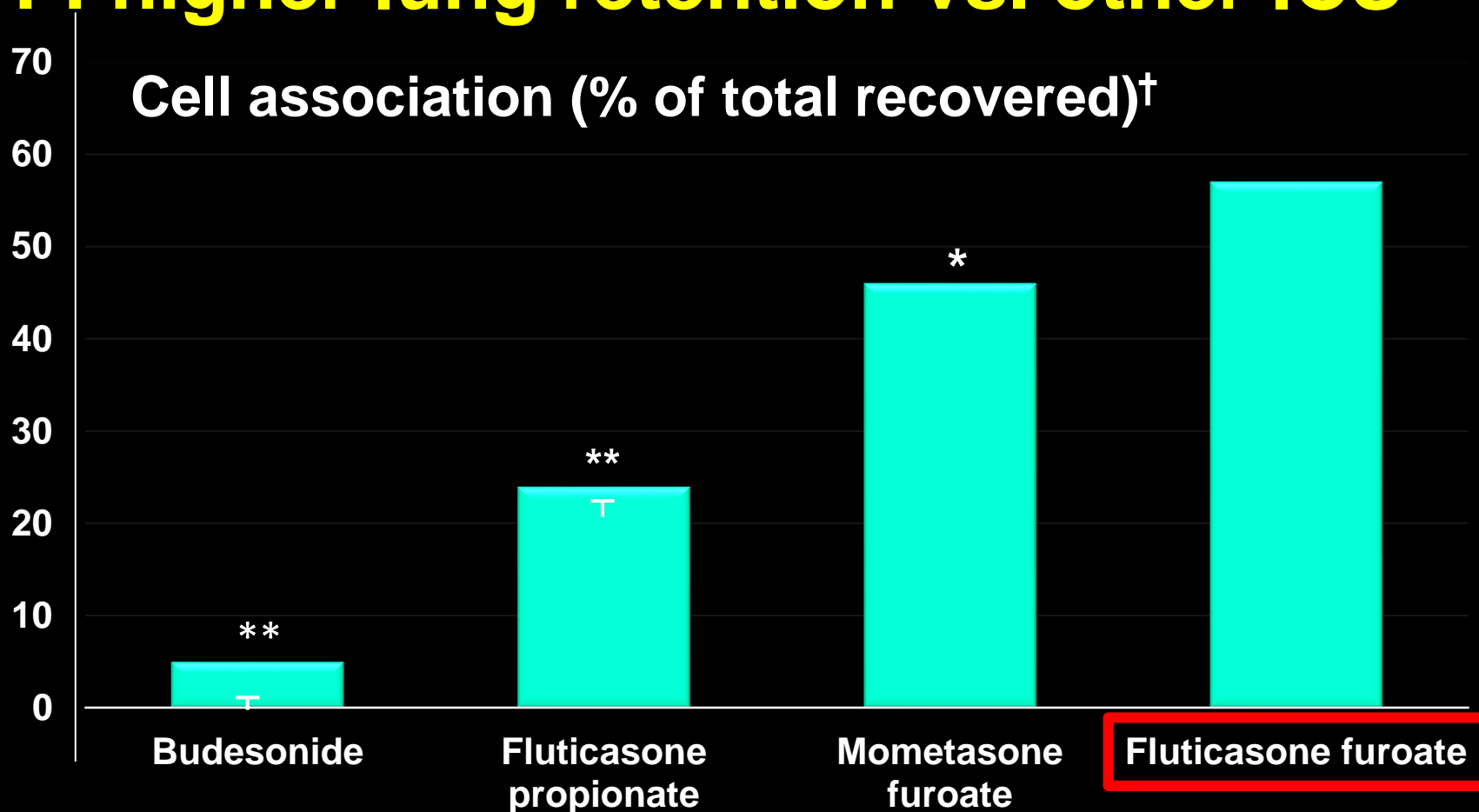
一般用法: 吸入1劑 QD



GR Binding affinity of different ICSs



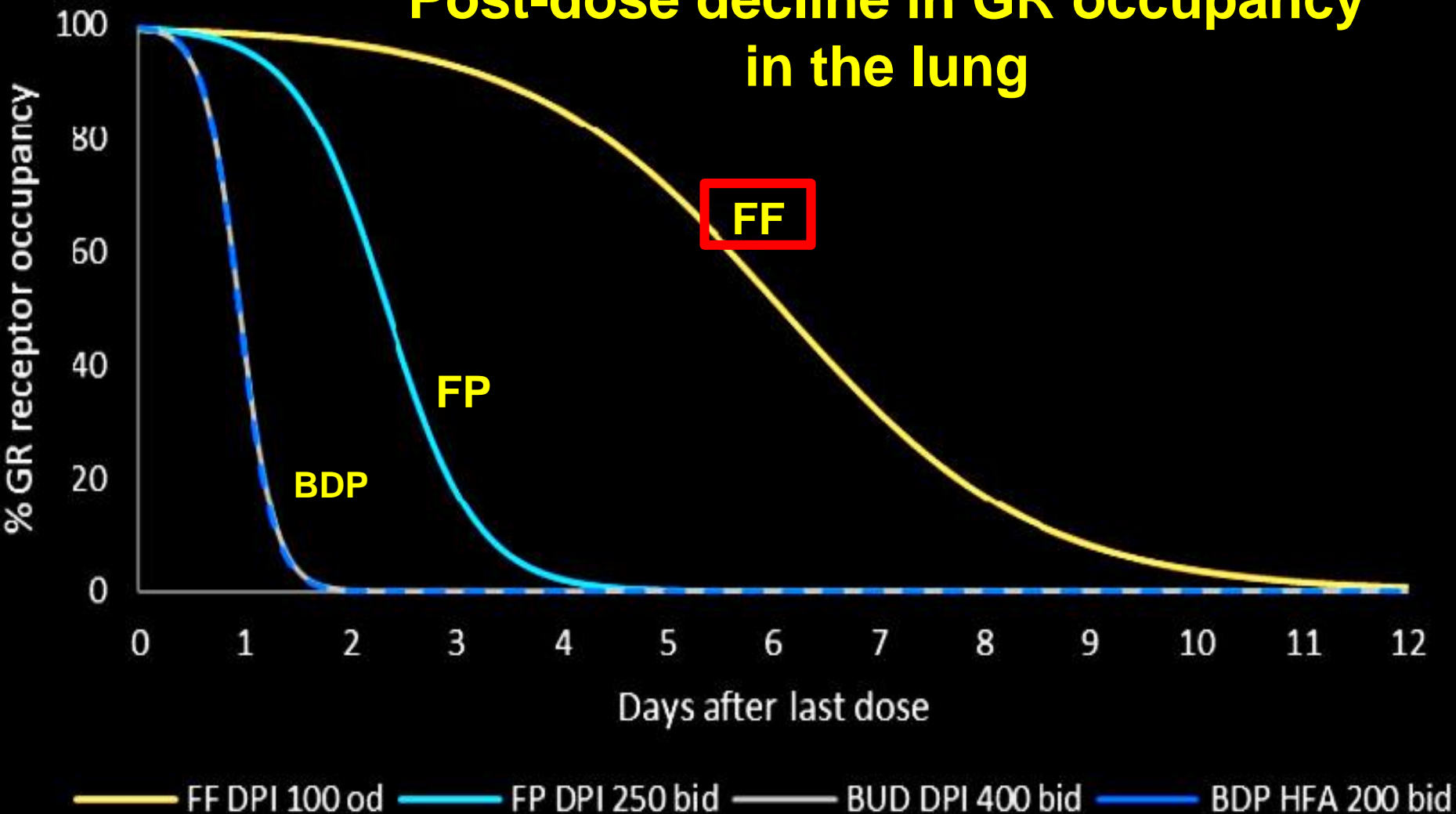
FF: higher lung retention vs. other ICS



* $P < 0.05$ versus FF; ** $P < 0.01$ versus; [†]Study design: using a monolayer of human lung epithelial (16HBE14o) cells. Cell association of ICS at the cell monolayer was determined and quantified as total recovery.

Salter M et al. Am J Physiol Lung Cell Mol Physiol. 2007;293:L660–667.

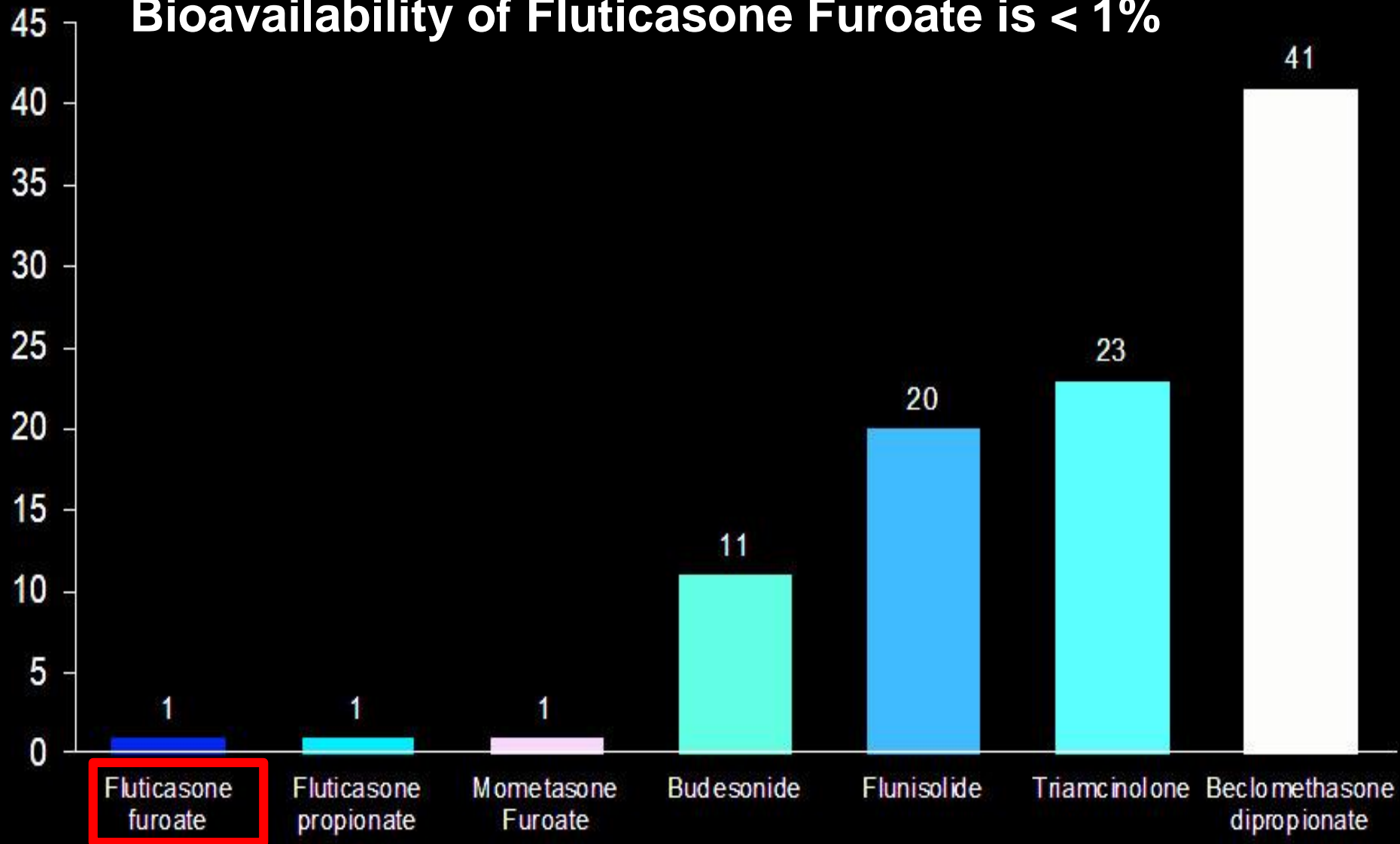
Post-dose decline in GR occupancy in the lung



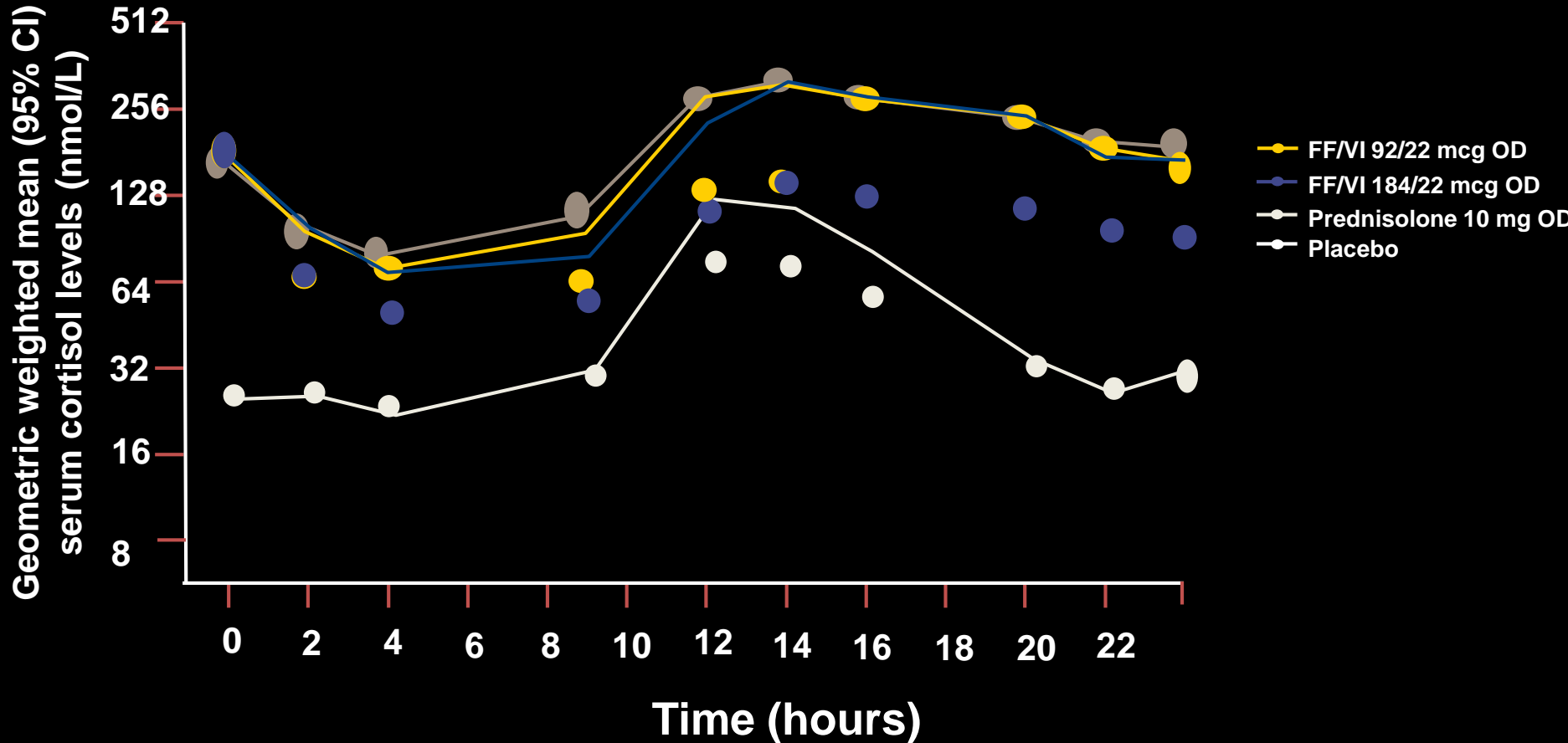
GR Occupancy values : theoretical maximum achievable assuming optimal drug delivery and tissue distribution in the lung and the lung bioavailable dose fully accessible for GR binding during dosing to steady state.

Bioavailability: FF vs. other ICS molecules

Bioavailability of Fluticasone Furoate is $< 1\%$



Serum cortisol: FF has no significant effect at 42 days (n = 185)



Serum cortisol levels were notably lower in the prednisolone

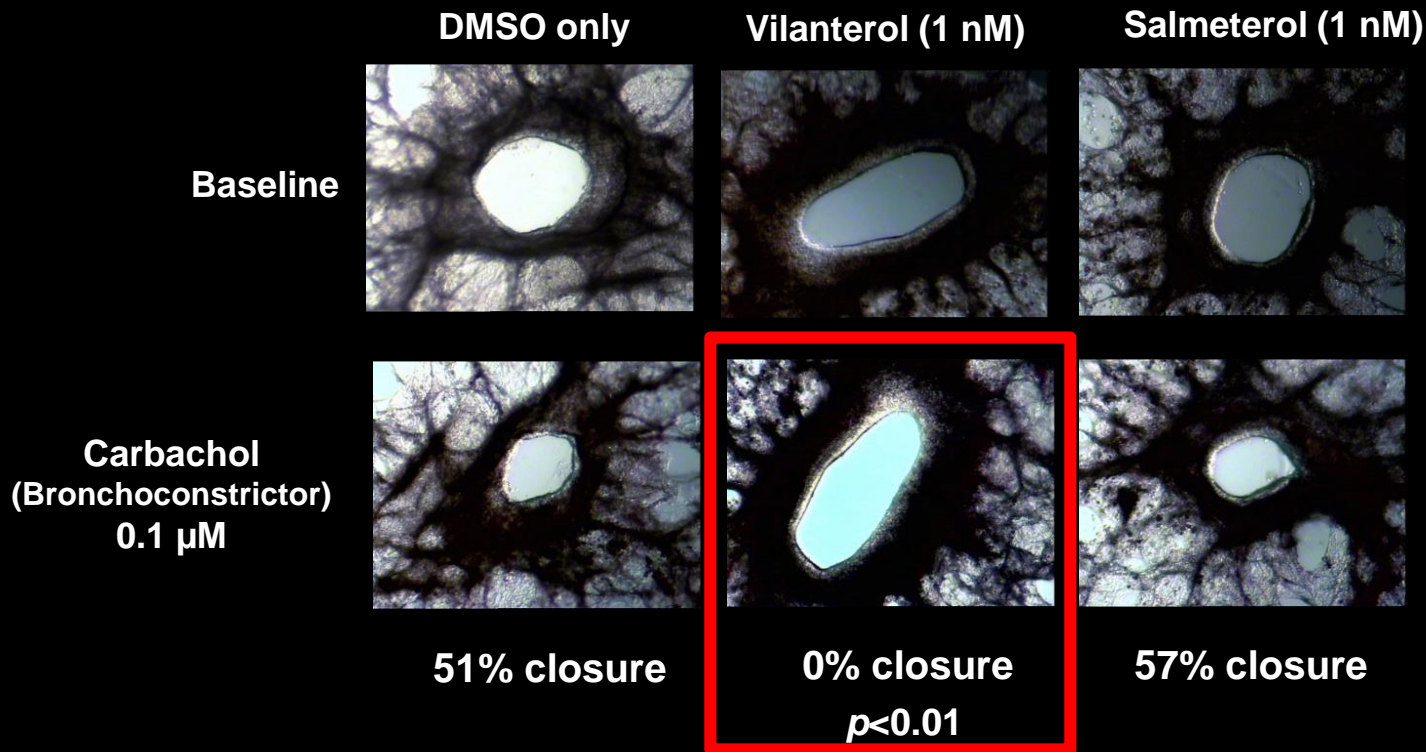
Vilanterol (VI): Once-daily bronchodilator

In-vitro data

Affinity for β_2-AR	= salmeterol > formoterol > Indacaterol
Persistence of action at β_2-AR	= indacaterol > formoterol
Selectivity of β_2-AR (vs β_1 and β_3)	> formoterol > indacaterol = salmeterol

Vilanterol is not licensed as monotherapy.

Vilanterol: Longer duration of action than salmeterol



in-vitro data

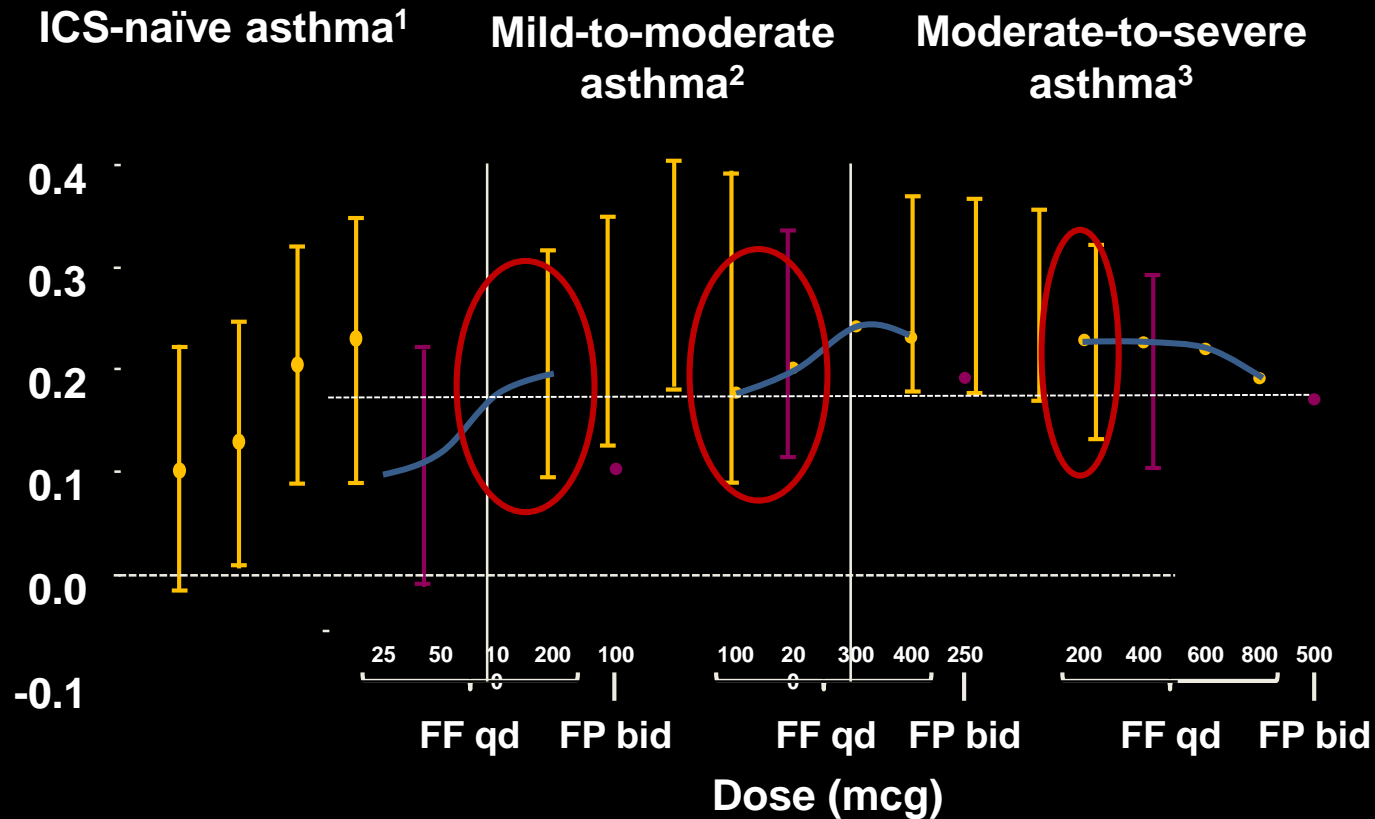
Dose and Dosing

- QD



The optimal doses of FF: 100 and 200 μg

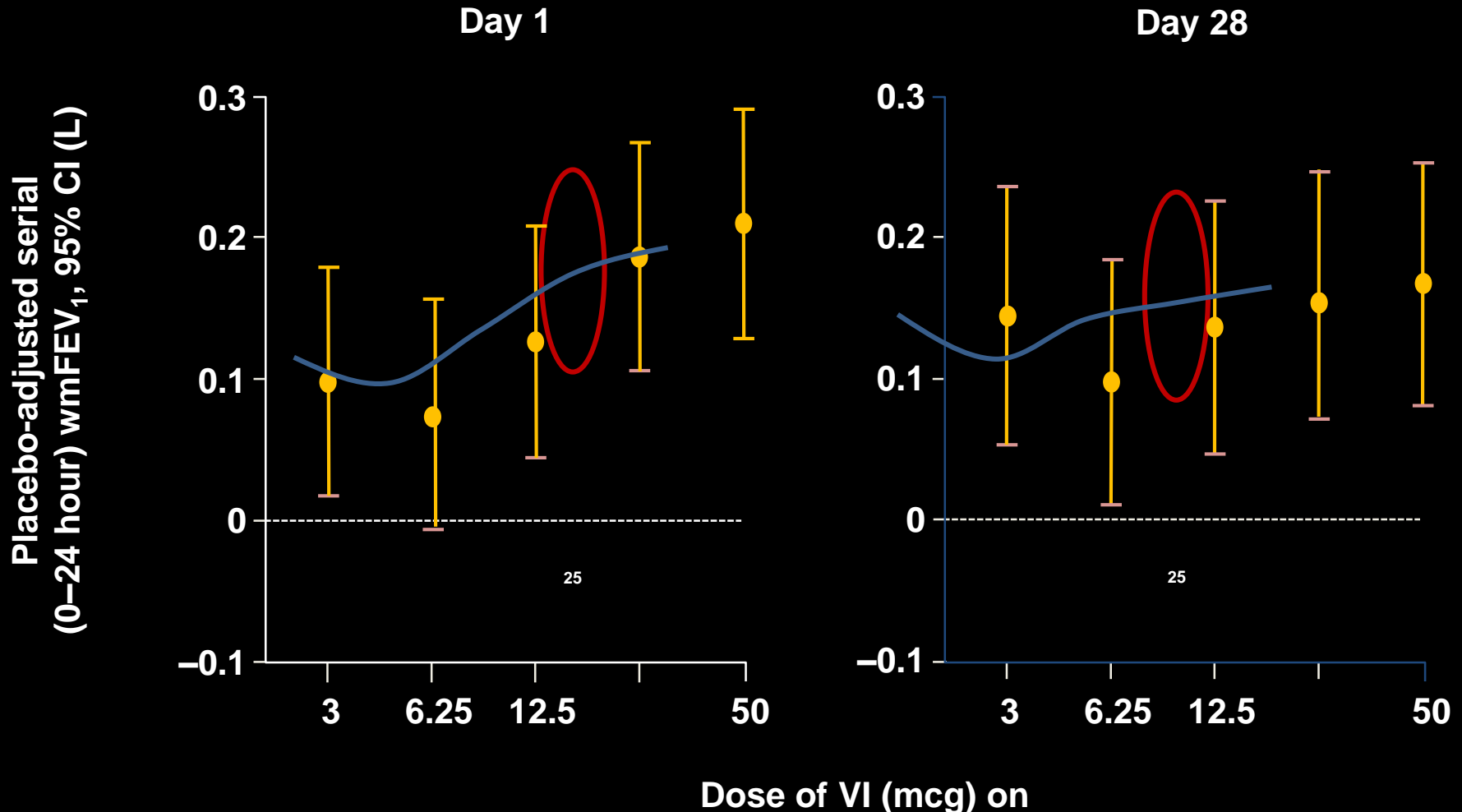
Trough FEV₁ at Week 8 in 3 phase II studies in asthma



1. Bateman ED et al. *Respir Med.* 2012;106:642–650; 2. Bleecker ER et al. *Ann Allergy Asthma Immunol.* 2012;109:353–358; 3. Busse WW et al. *Thorax.* 2012;67:35–41.

The optimal dose of VI: 25 μg

Lung function in asthma assessed by weighted mean FEV_1



Q

(A or B) FF/VI (Relvar) 100/25 之 ICS strength 屬於 :

A. Low dose ICS

B. Medium dose ICS

C. High dose ICS



Low, medium and high dose ICSs (≥ 12 years)

	Low	Medium	High
Beclometasone dipropionate (CFC)	200–500	>500–1000	>1000
Beclometasone dipropionate (HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100	n.a.	200
Fluticasone propionate (DPI or HFA)	100–250	>250–500	>500
Mometasone furoate	110–220	>220–440	>440
Triamcinolone acetonide	400–1000	>1000–2000	>2000

- This is not a table of equivalence, but of estimated clinical comparability
- Most of the clinical benefit from ICS is seen at low doses
- High doses are arbitrary, but for most ICS are those that, with prolonged use, are associated with increased risk of systemic side-effects

Low, medium and high daily doses of ICS

Inhaled corticosteroid	Daily doses (μg) (≥ 17 years)		
	Low	Medium	High
Beclometasone dipropionate (CFC) [†]	200–500	600–1000	1200 – 2000
Beclometasone dipropionate (HFA)	100–200	300–400	500 – 800
Budesonide (DPI)	200–400	600–800	1000 – 1600
Ciclesonide (HFA)	80–160	240–320	400 – 640
Fluticasone furoate (DPI)	N/A	100	200
Fluticasone propionate (DPI)	100–250	300–500	600 – 1000
Fluticasone propionate (HFA)	100–250	300–500	600 – 1000
Mometasone furoate	200	400	800

Device

- Ellipta



Ellipta : 2003年左右開始研發，歷經十年於2013年上市

Diskus



- One 60-dose blister strip
- 'Blended' technology for combination products

Ellipta



- Two 30-dose foil blister strips for combination products
- Individual formulation development

Ellipta - designed for simplicity and ease of use

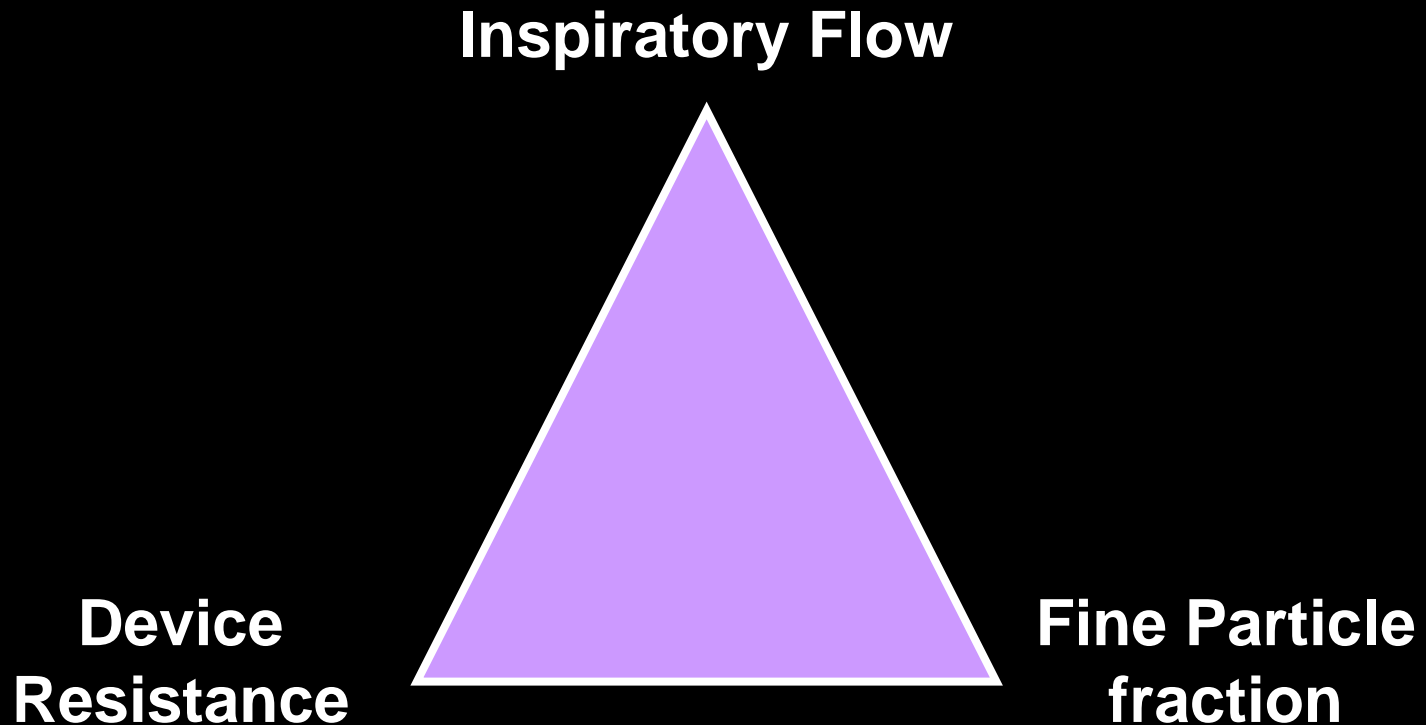


Ellipta操作步驟

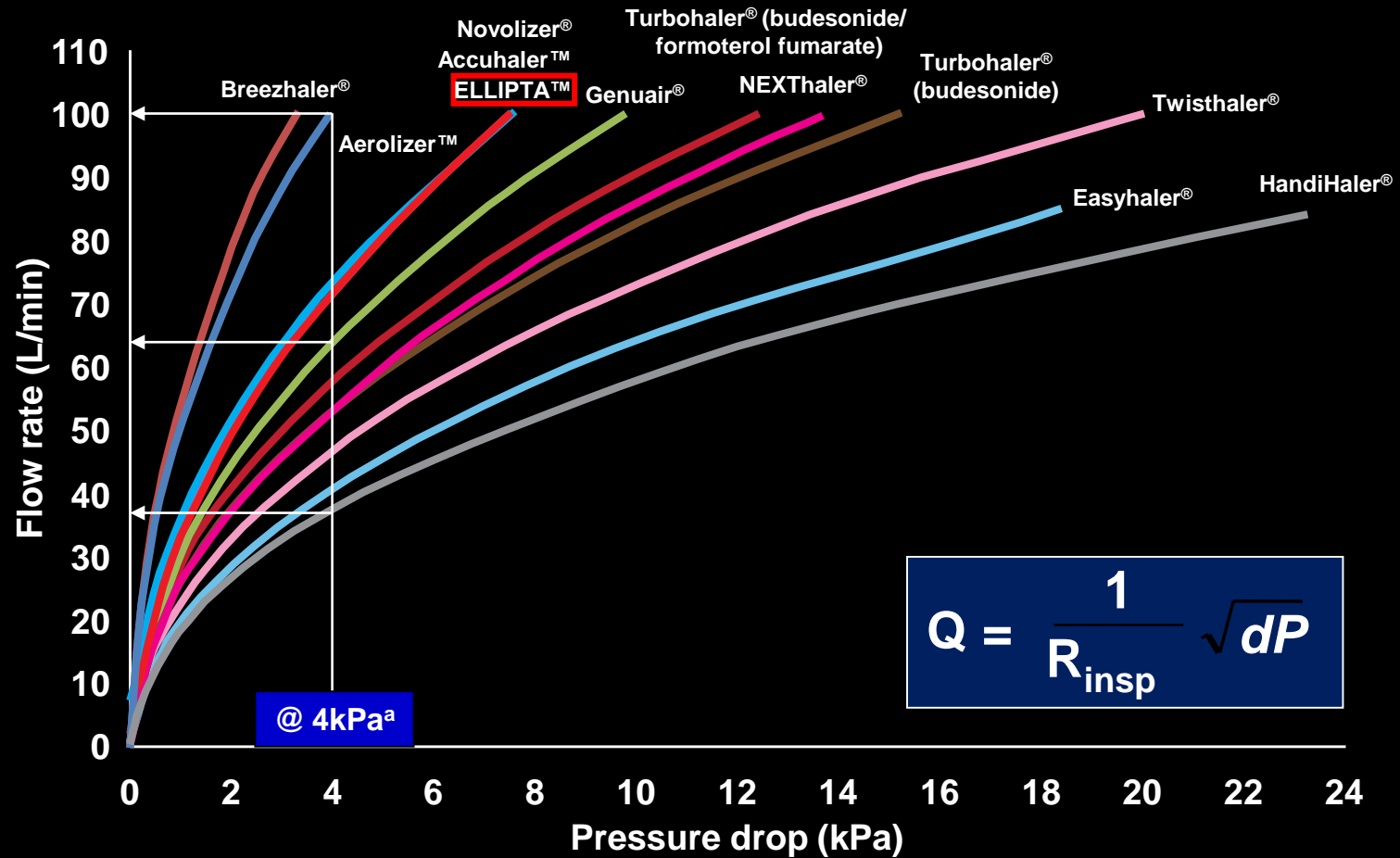
- 完全打開吸口蓋 (聽到「卡嗒」聲)，劑量計數器會遞減數字，確認已上好一劑藥物。



DPI: Evaluating Drug Delivery



Ellipta: Medium resistance DPI



^atypical pressure drop for DPI testing, rated to be achievable and relevant for COPD and asthma patients

Phillip Krüger. 2014 at ERS International Congress

Internal resistance of DPI vs. FPF

- Devices with low variability and medium inspiratory resistance can combine the positive aspects of
 - Achievable flow rates
 - Consistent and efficient fine particle generation
 - Reduced impaction losses in the upper airways

Low resistance

→ higher flow rate

→ higher FPD

→ higher impaction losses

**Medium
Resistance**

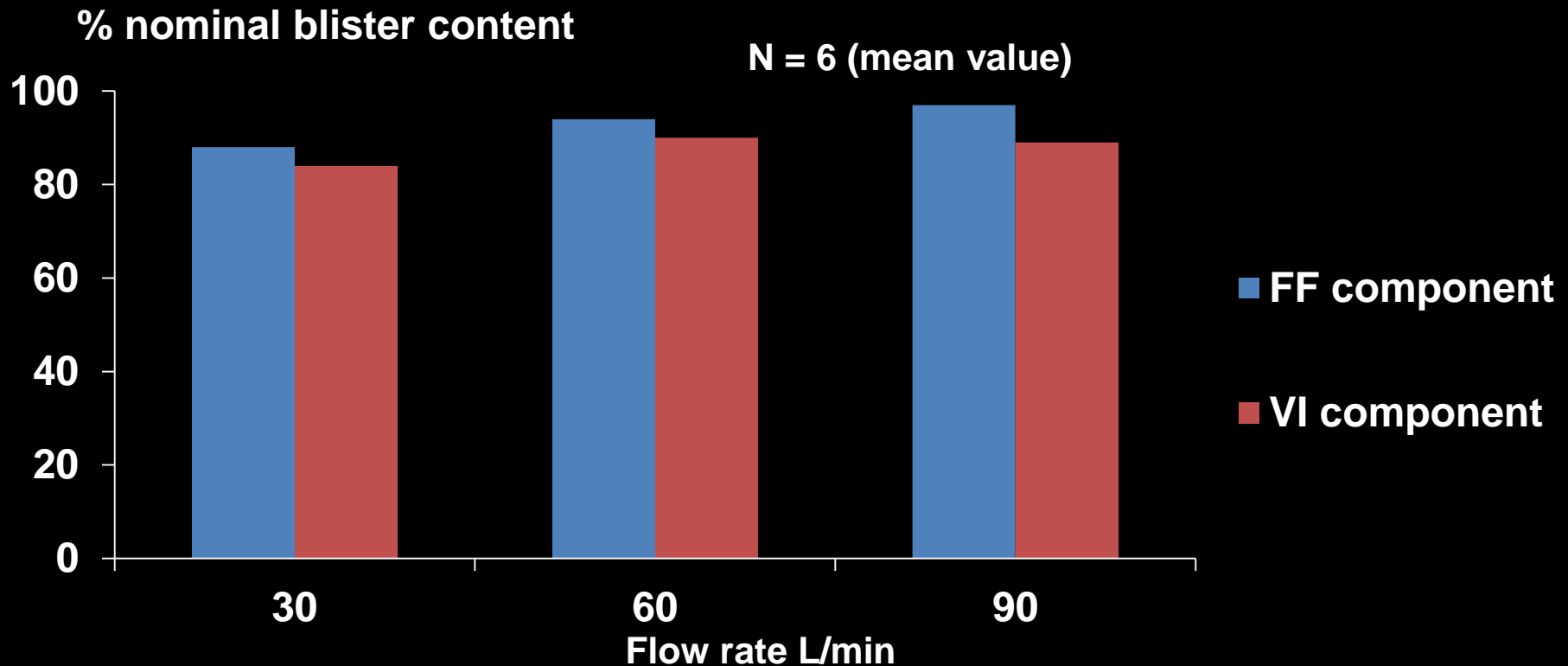
High Resistance

→ lower flow rate

→ lower impaction losses

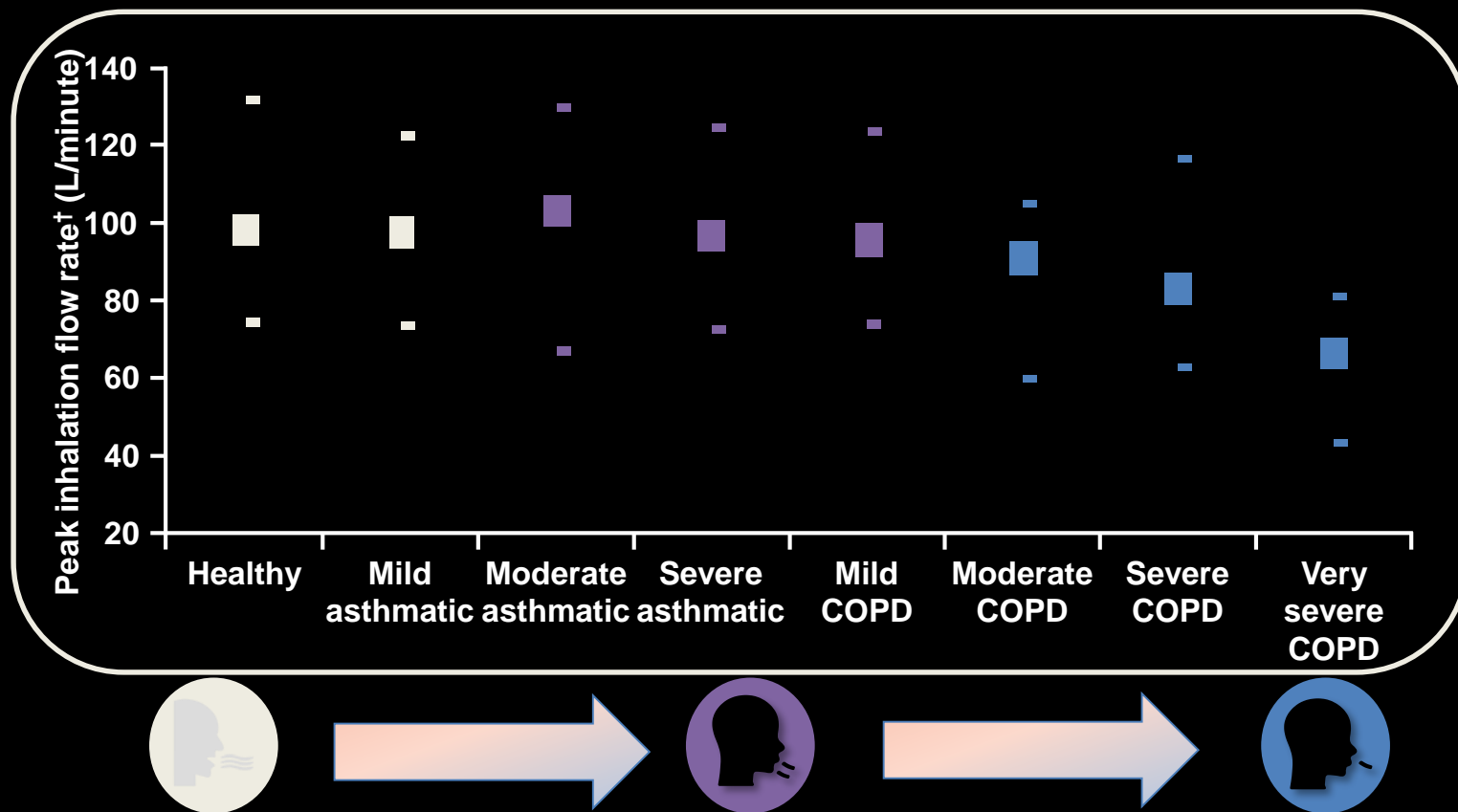
→ lower FPD

Elliptas: *in vitro* dose delivery across flow rates of 30, 60 and 90 L/min



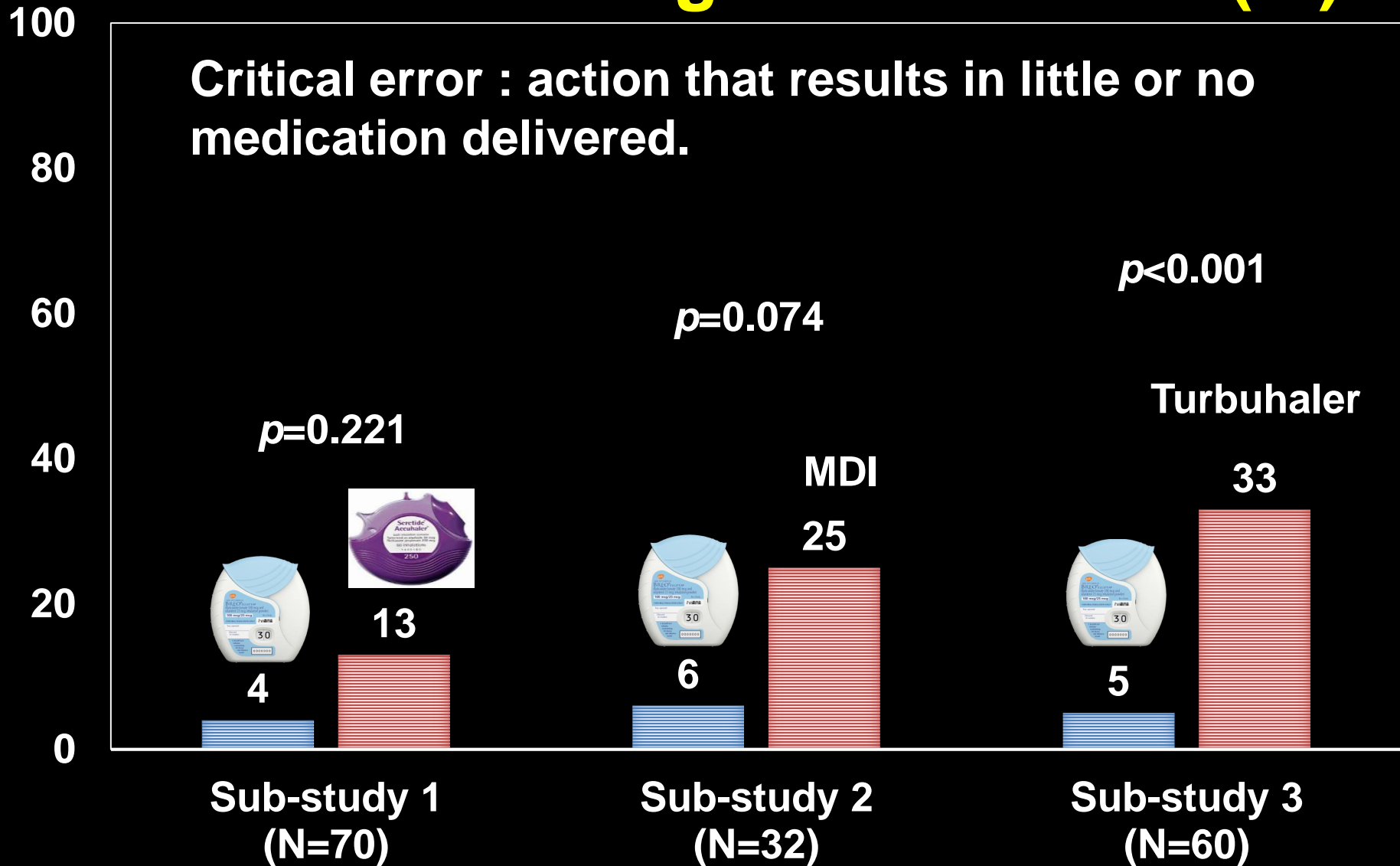
	MMAD (range) (microns)
FF	4.0 (3.6 – 4.8)
VI	2.3 (2.0 – 2.6)

Ellipta: Suitable for patients with mild asthma through to very severe COPD



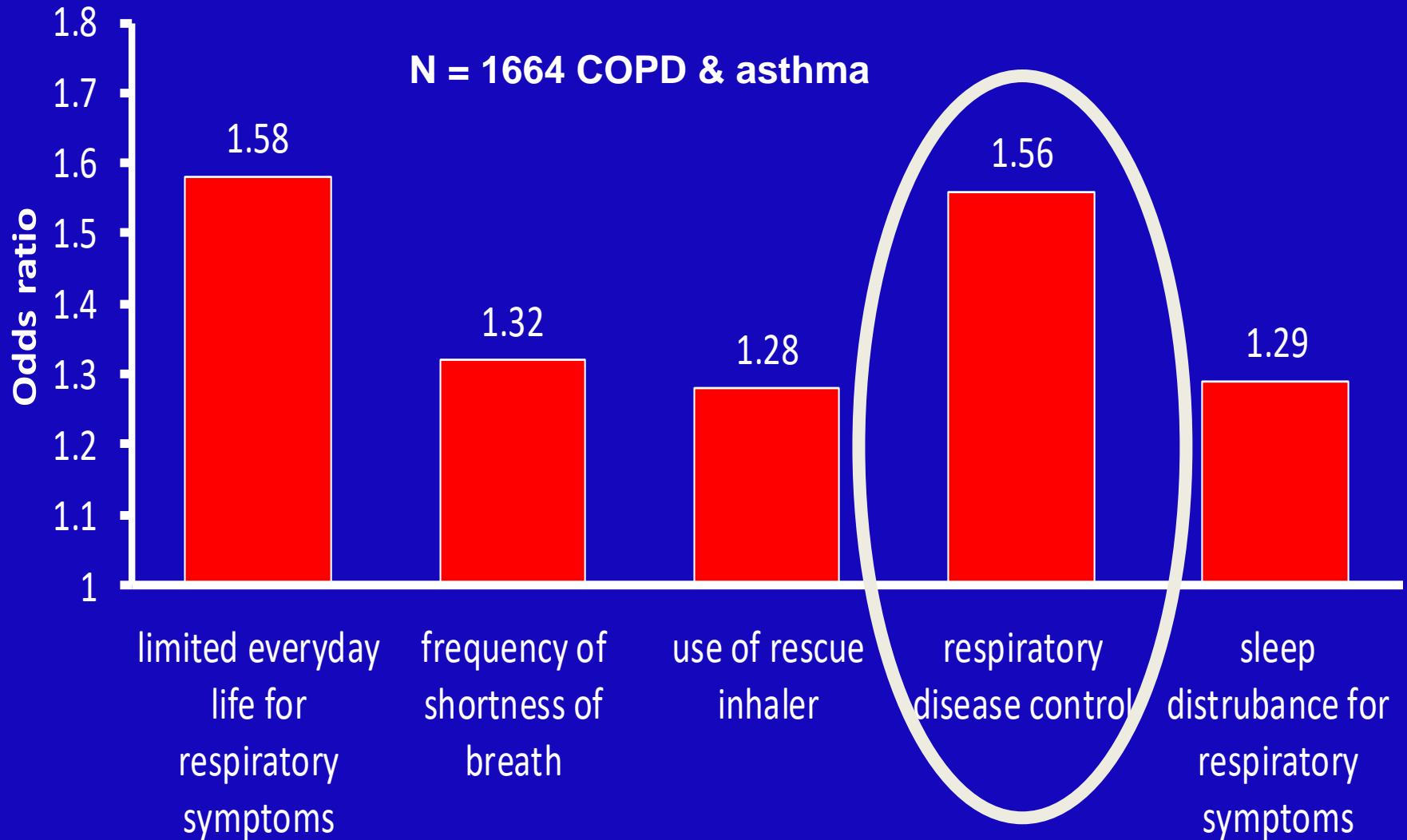
†Mean and absolute range. Disease severity categorised by GINA and GOLD guidelines (very severe COPD: $FEV_1/FVC < 70\%$, $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure).

Patients making critical errors (%)

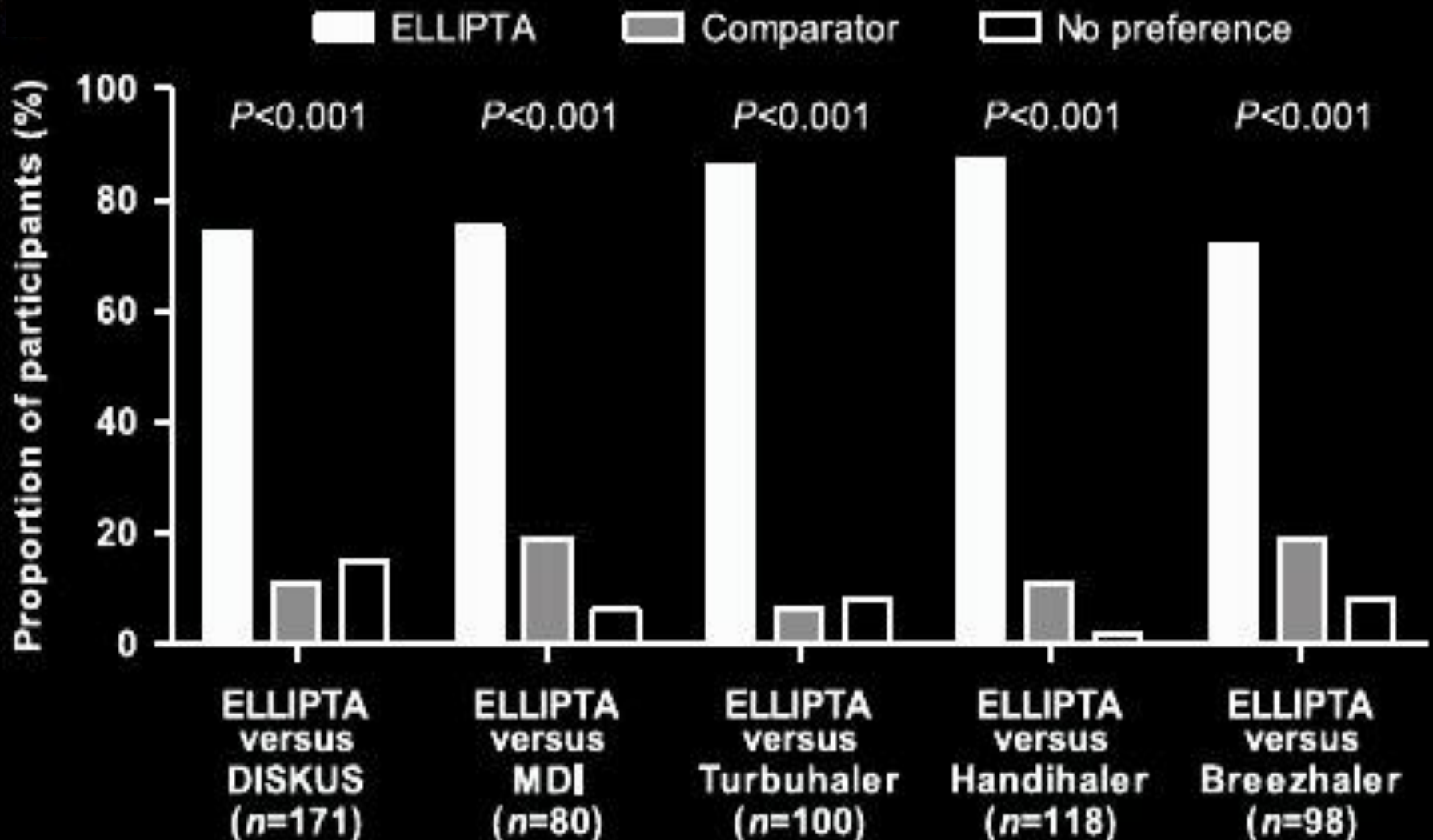


Inhaler Mishandling vs. Poor Disease Control

Critical Inhaler Error



Device preference

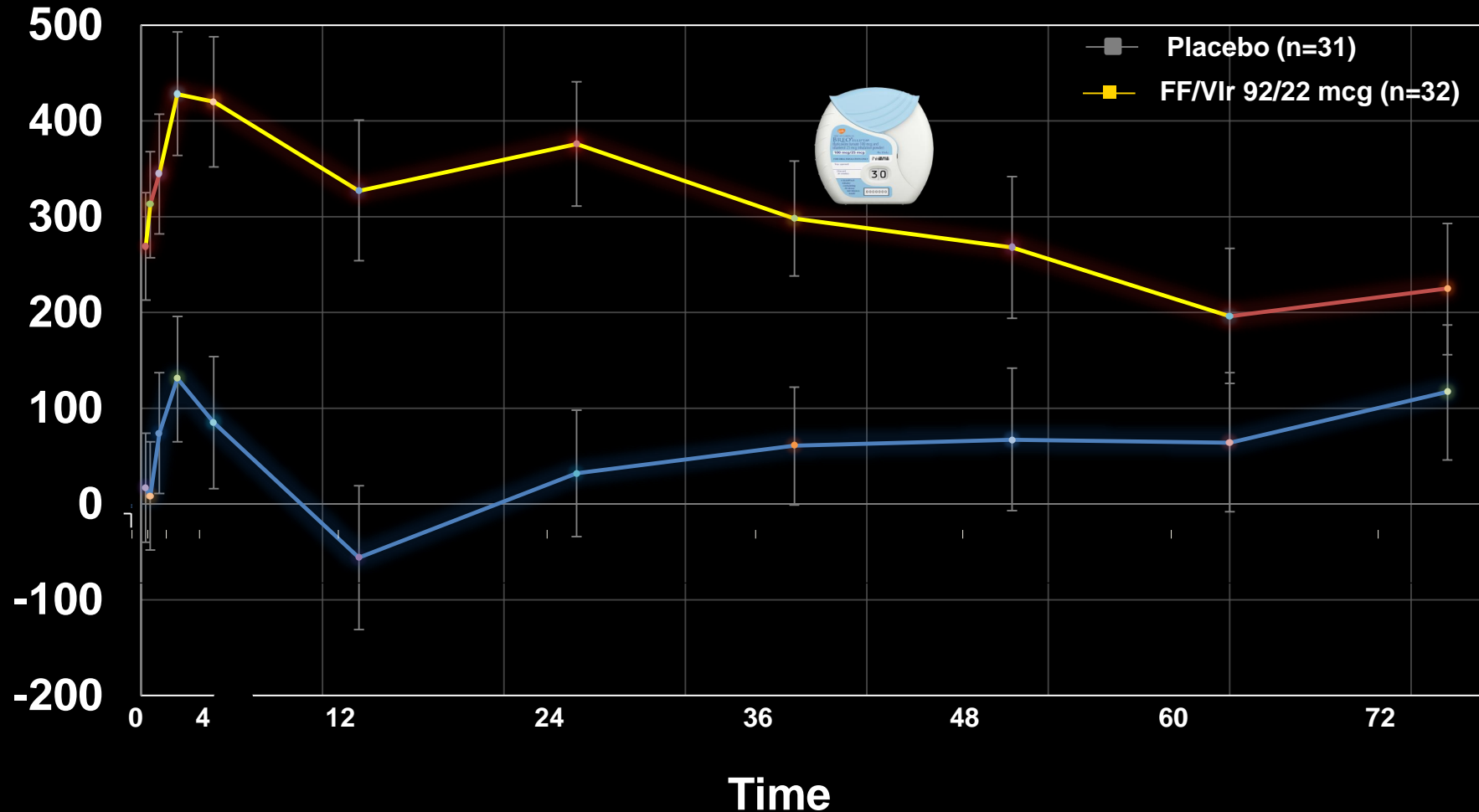


Clinical benefits in asthma



FF/VI: Bronchodilation seen at 15 minutes and sustained over 72 hours

Changes in FEV1





FEV₁ : FF/VI qd vs. FP/SAL bid

A double blinded RCT

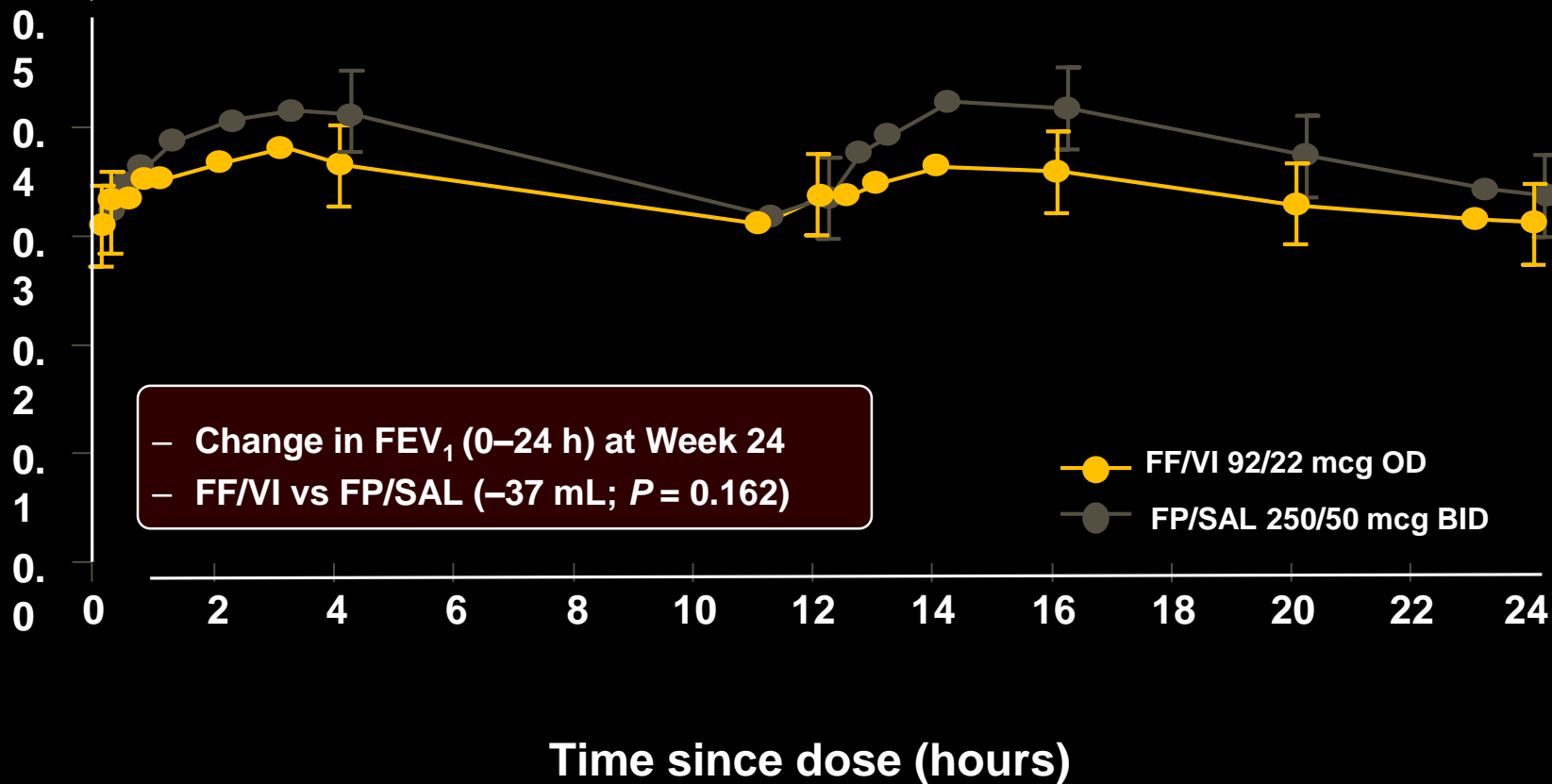
FP/SAL



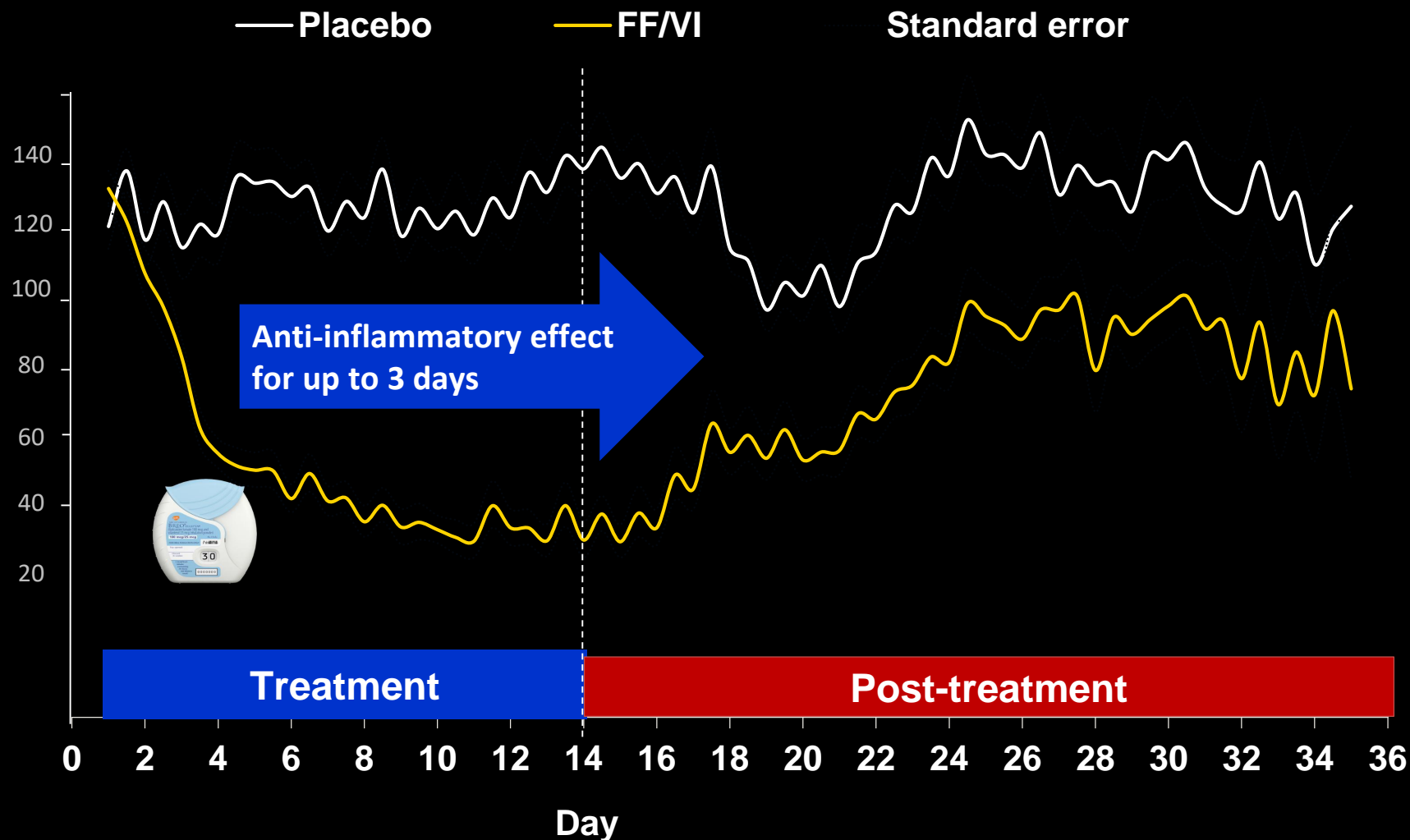
EE/VI



Changes in FEV₁ (0–24 h)



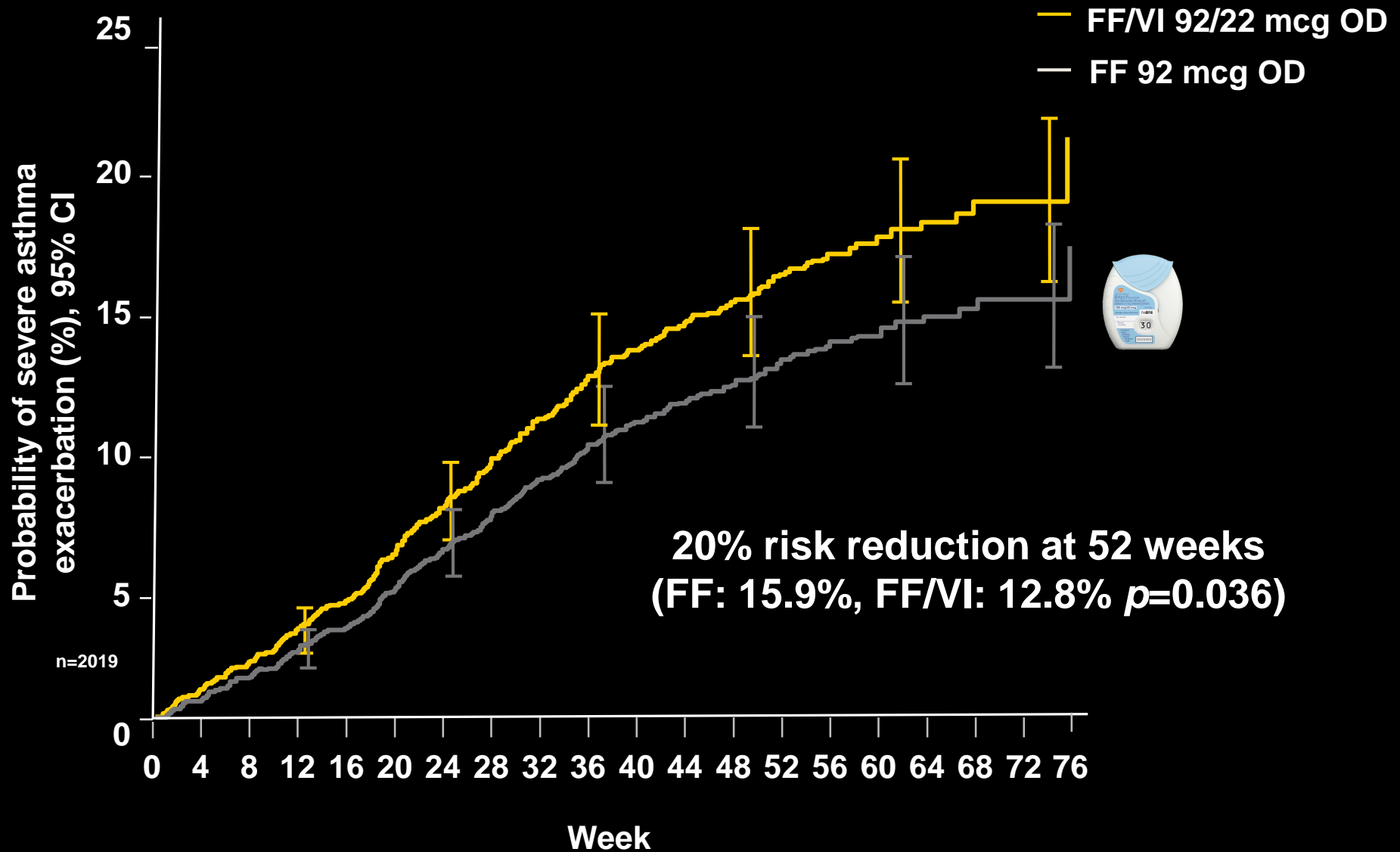
FeNO: FF/VI has anti-inflammatory effect for up to 3 days



Patients: steroid naive

Bards: ey G et al. *Resp Res* 2018; 19:133

Severe asthma exacerbation: FF/VI vs. FF



FF/VI vs Usual Care



Study Design

- ≥18 years
- Primary care
- GP diagnosis of asthma

- Open-label treatment period (52 weeks)
- Normal care
 - Constant real-time data collection

Maintenance inhaler

FF/VI 92/22 or 184/22 µg OD

Existing maintenance therapy*

n= 4,233

Week 0

Week 24

Week 52

Existing maintenance therapy includes ICS and ICS/LABA

ACT administered 5 times

Responder的定義

N = 4233.



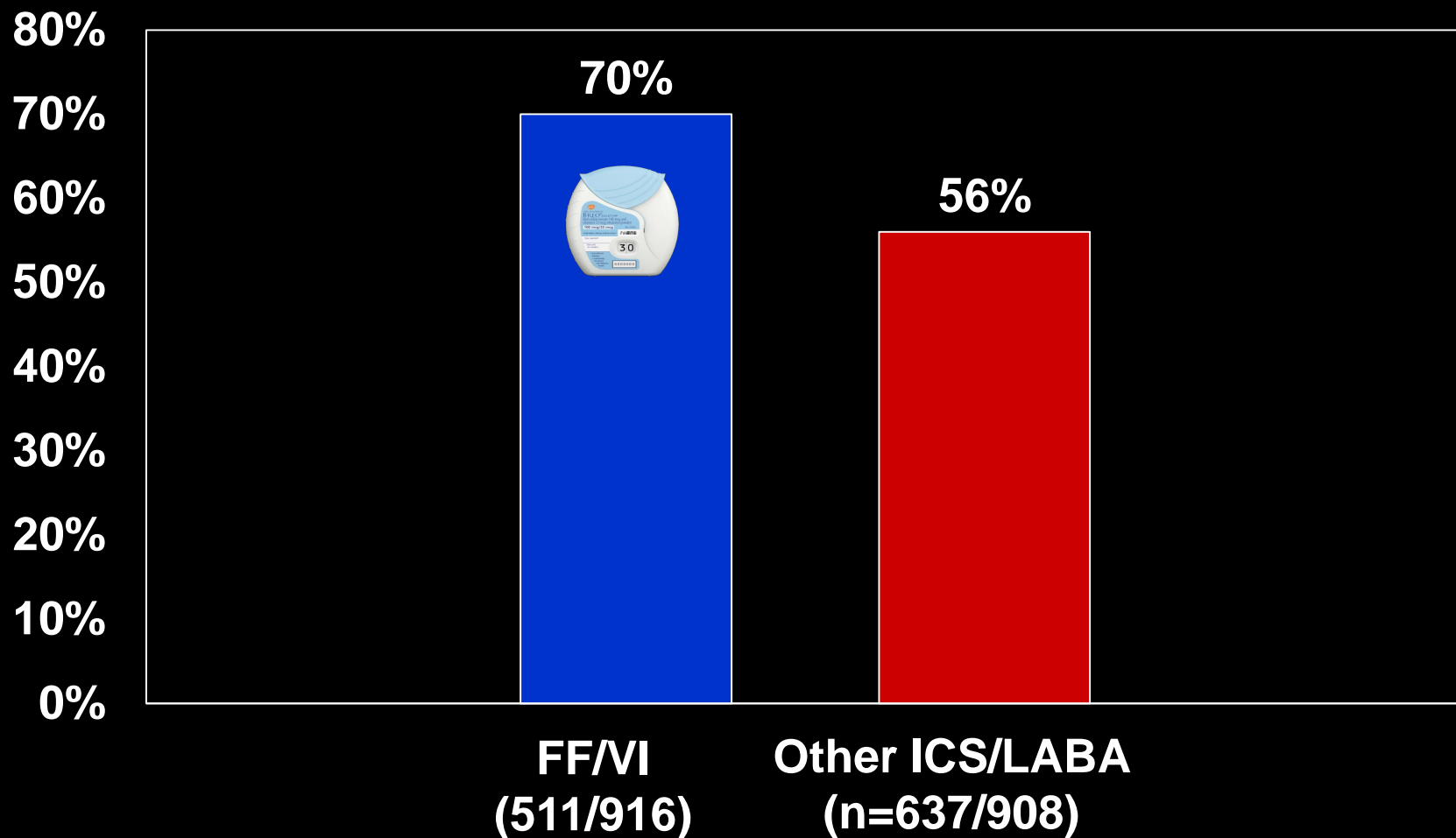
在第24週(6個月)時，達到ACT total ≥ 20 和ACT進步 ≥ 3 的比例

(ACT進步 ≥ 3 在臨床上達到MCID)

Patients' Characteristics

		Usual Care (N = 2119)	FF/VI (N=2114)	Total (N=4233)
Age (years)	≥ 50	49.7 (16.7)	49.9 (16.1)	49.8 (16.4)
Sex	Female	59%	59%	59%
Smoking status	Current	20%	20%	20%
	Former	34%	31%	33%
	Non smoker	46%	49%	47%
BMI (kg/m ²)	≤ 30	57%	58%	57%
	> 30	43%	42%	43%
ACT Total Score at Baseline	≥ 20	29%	28%	28%
	16 to 19	31%	31%	31%
	≤15	41%	41%	41%

ACT responders: FF/VI vs. other ICS/LABAs



Asthma control : FF/VI vs. usual care

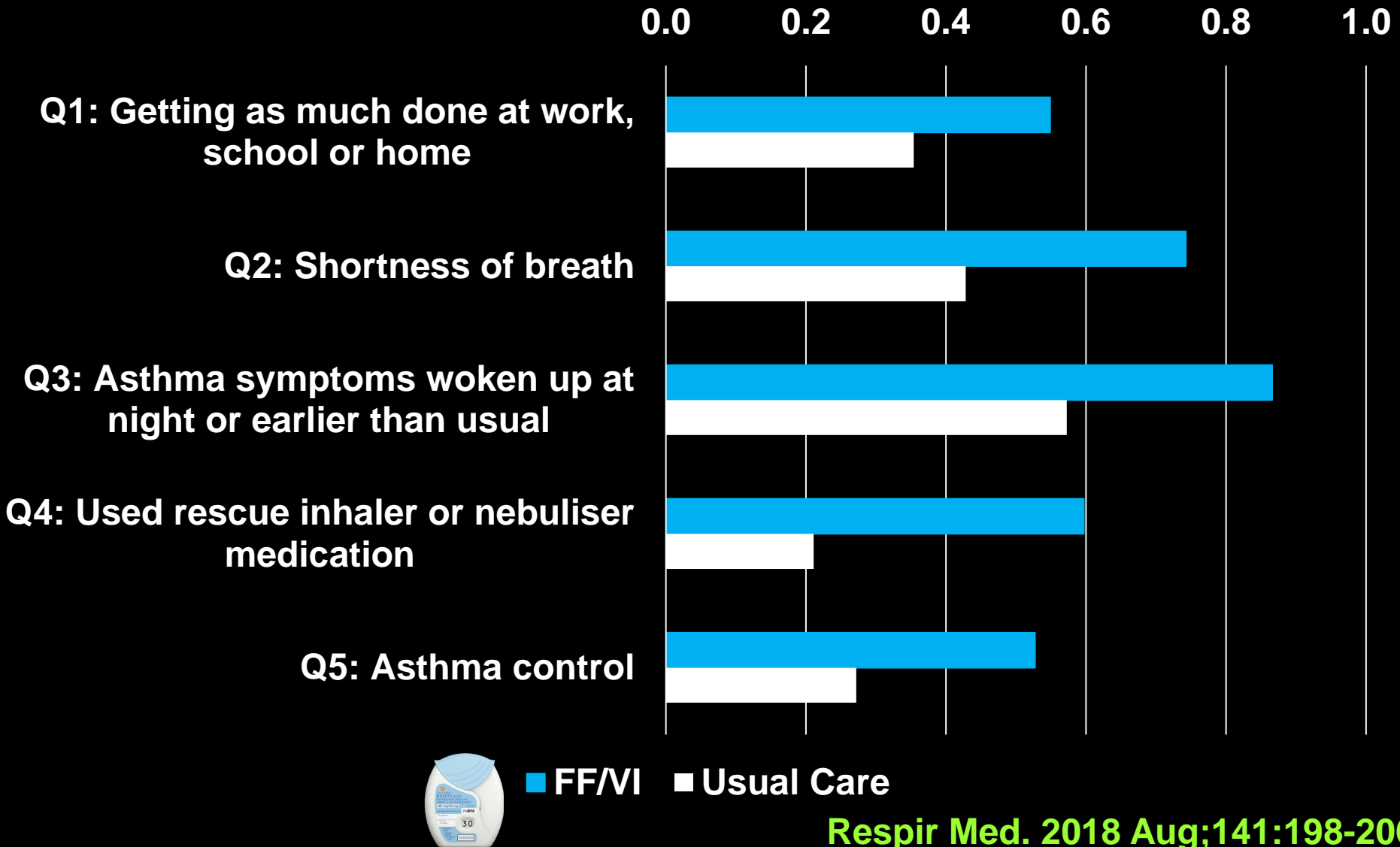
Primary Effectiveness Analysis (PEA) Population



	Usual Care (N=1514)	FF/VI (N=1512)
n	1399	1373
Responder	784 (56%)	977 (71%)
Non-Responder	615 (44%)	396 (29%)
FF/VI vs. Usual Care Adjusted Odds Ratio		2.00
95% CI		(1.70, 2.34)
p-value		<0.001

Woodcock A et al. *Lancet* 2017; 390:2247–2255.

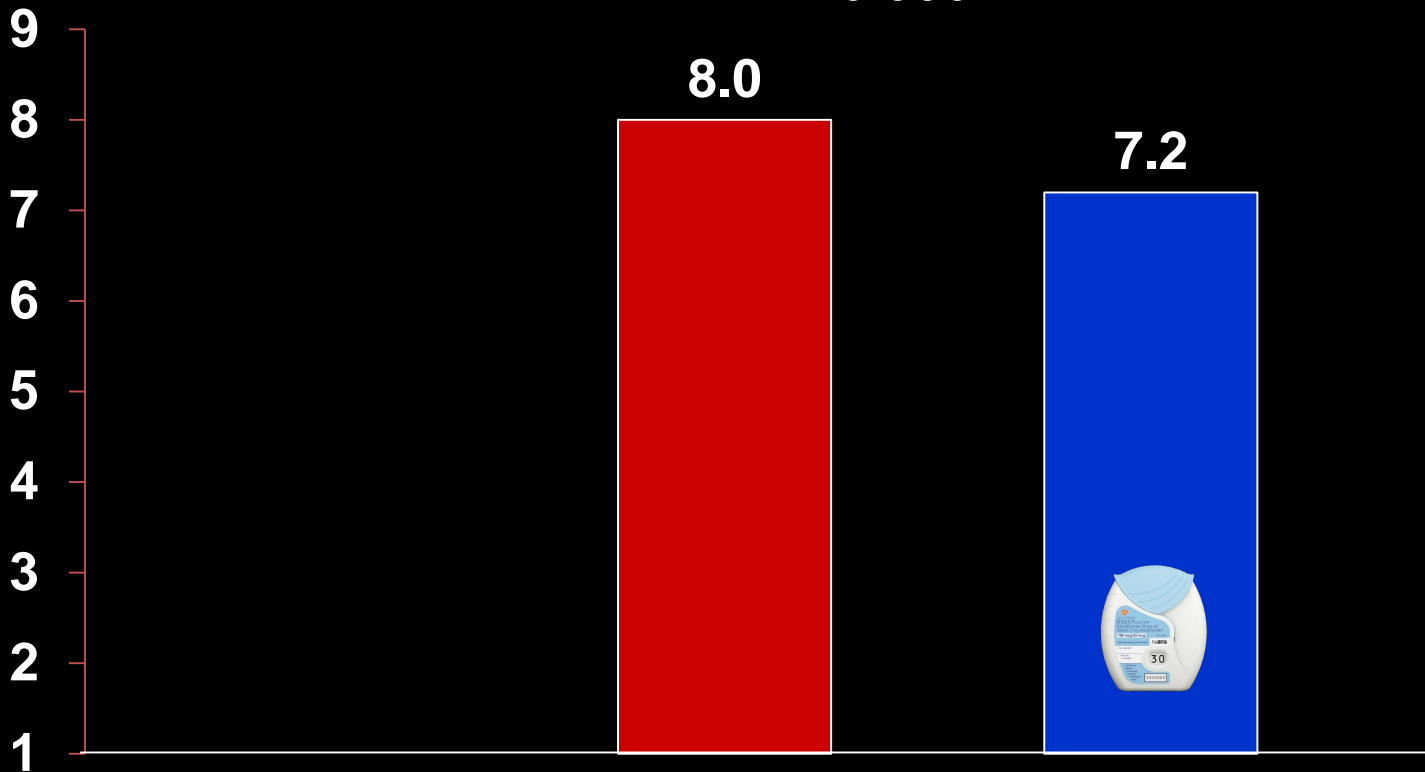
Δ ACT score: FF/VL vs. Usual Care



SABA use: FF/VI vs. usual care

inhalers

$P < 0.0001$

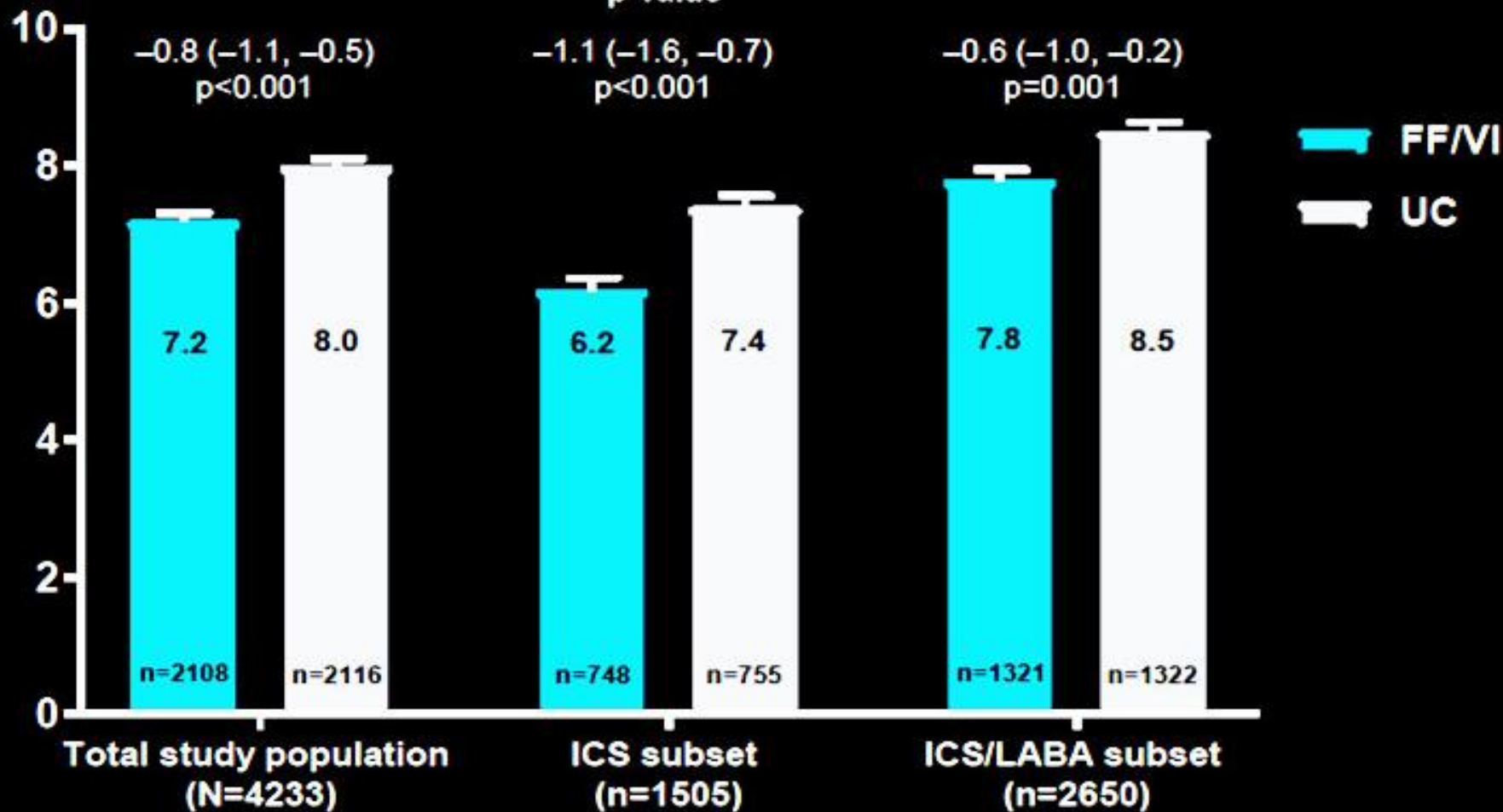


■ Usual Care
(N = 2119)

■ FF/VI
(N = 2114)

SABA's Usage : FF/VI vs. Usual Care

Difference FF/VI vs UC (95% CI)
p-value



FF/VI vs. FP/SAL in the Asthma Salford Lung Study

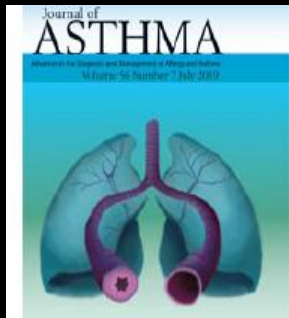
ISSN: 0277-0903 (Print) 1532-4303 (Online) Journal homepage: <https://www.tandfonline.com/loi/ijas20>

Effectiveness of fluticasone furoate/vilanterol versus fluticasone propionate/salmeterol on asthma control in the Salford Lung Study

Loretta Jacques, Nawar Diar Bakerly, John P. New, Henrik Svedsater, James Lay-Flurrie & David A. Leather

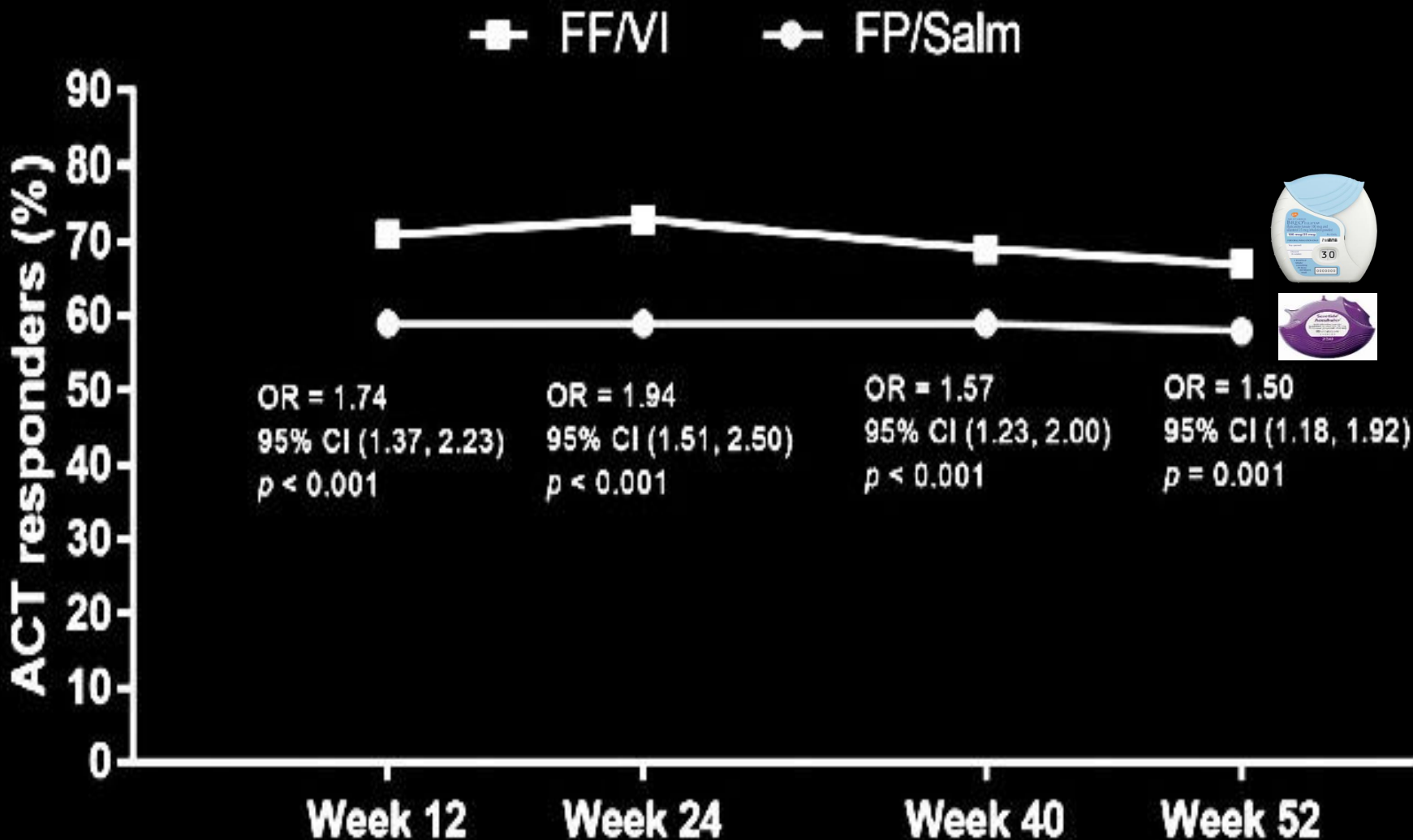
- FF/VI 646; FP/Salm 618
- ACT responder: 71% vs. 56%; OR 2.03 (1.53, 2.68); $p < 0.001$
- Benefits also observed in AQLQ responders, activity impairment due to asthma, exacerbation rates, and salbutamol inhalers prescribed.

Jacques L, et al. J Asthma. 2019 Jul;56(7):748-757



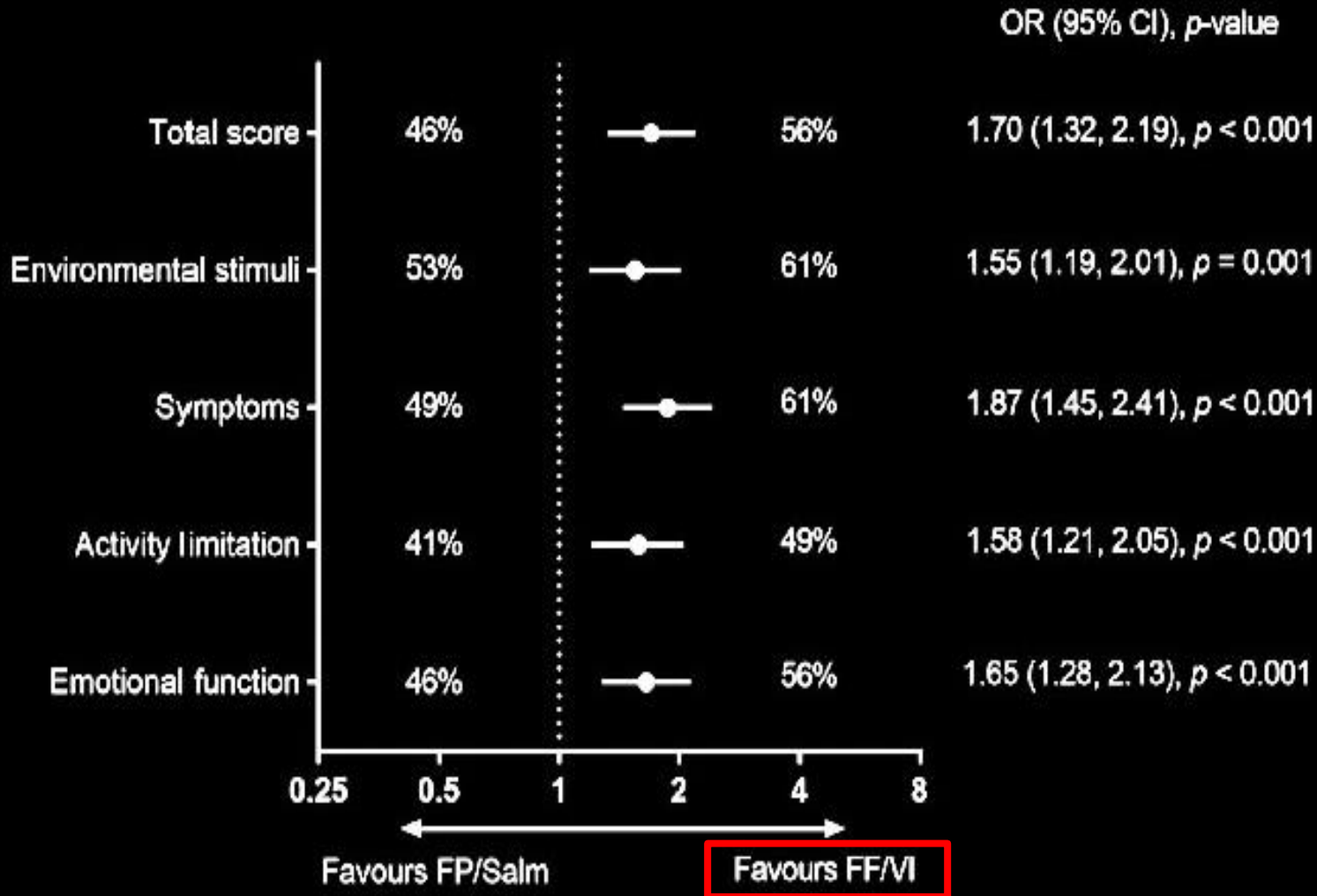


ACT Total Score Responders





AQLQ Score Responders

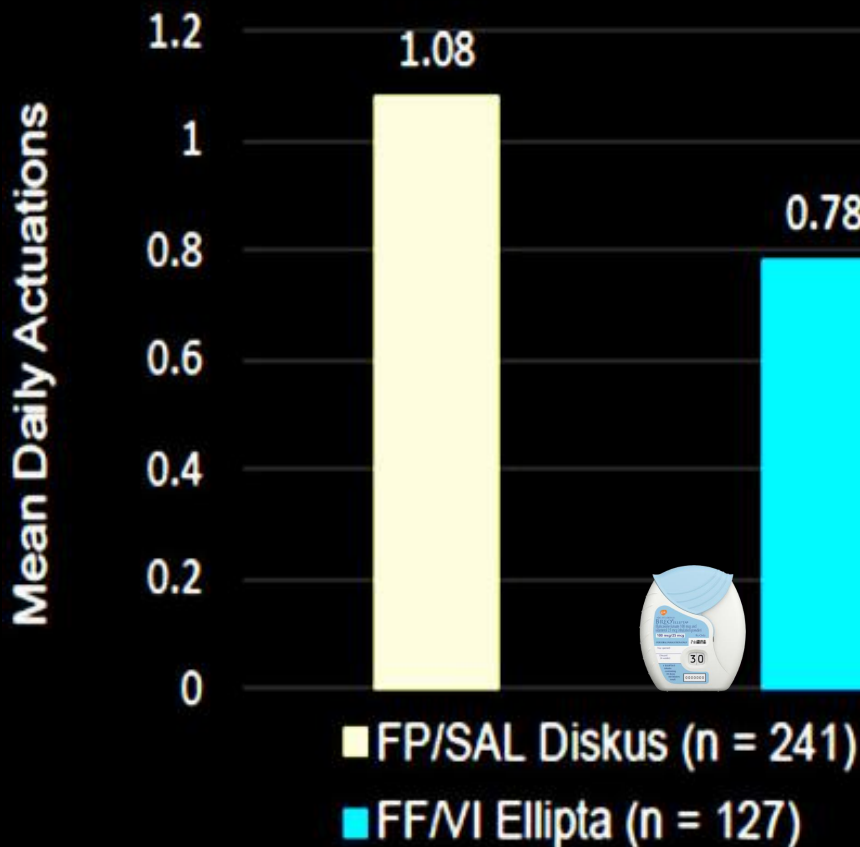




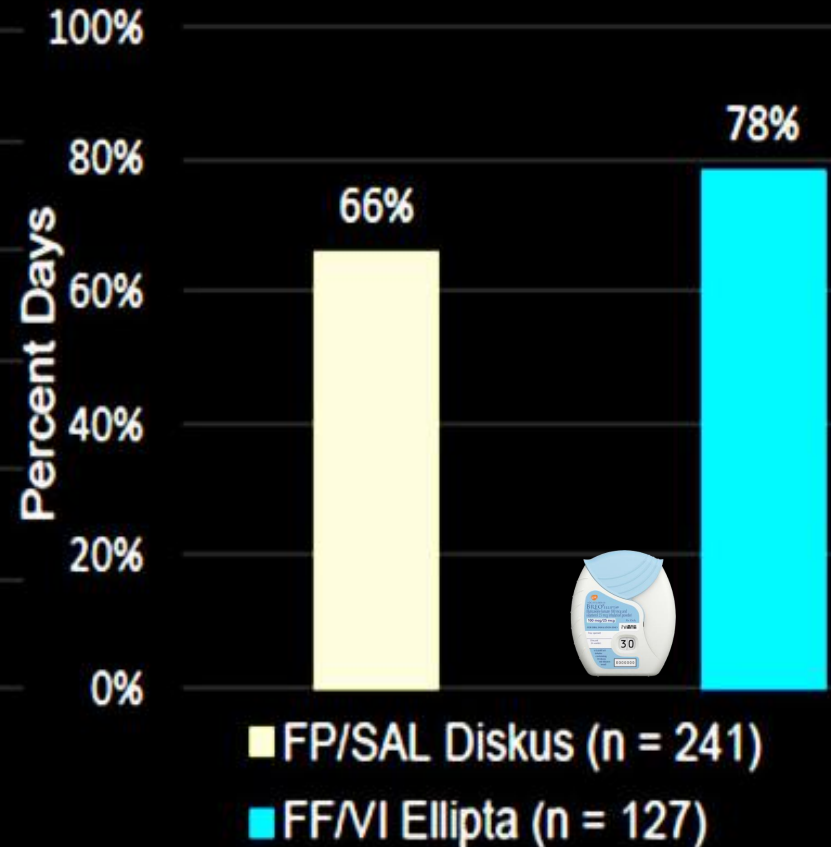
SABA use : FF/VI vs. FP/SAL

Sensor-derived SABA data over 6 months

Daily SABA usage



Percent SABA Free



FF/VI vs. BDP/FOR NEXThaler in asthma

Dal Negro et al. *Multidisciplinary Respiratory Medicine* (2018) 13:18
<https://doi.org/10.1186/s40248-018-0131-x>

Multidisciplinary
Respiratory Medicine

ORIGINAL RESEARCH ARTICLE

Open Access

Fluticasone furoate/Vilanterol 92/22 μg
once-a-day vs Beclomethasone
dipropionate/Formoterol 100/6 μg b.i.d.: a
12-month comparison of outcomes in mild-
to-moderate asthma



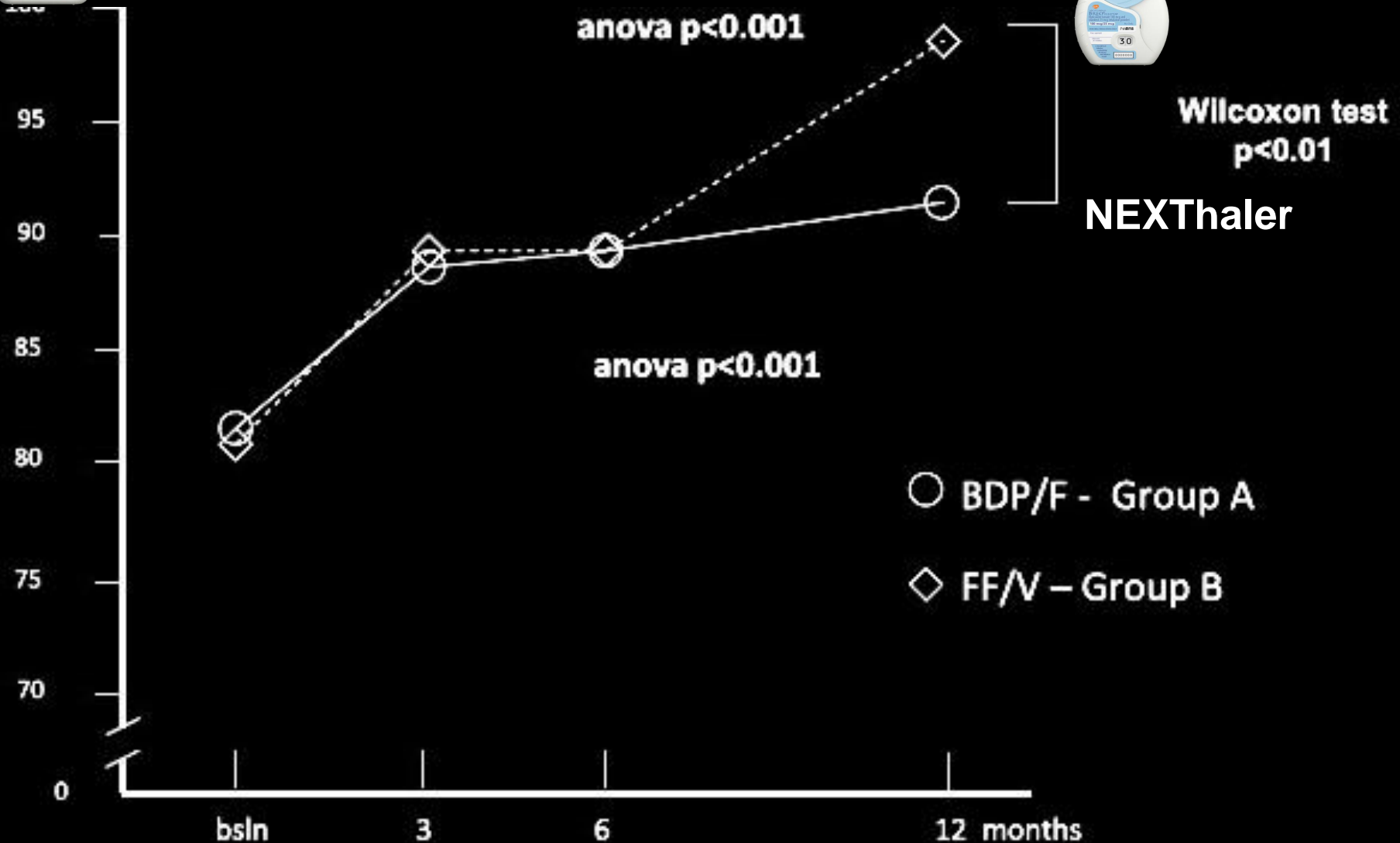
Roberto W. Dal Negro^{1*}, Luca Bonadiman¹ and Paola Turco²

- **PS-matching**



**BDP/FOR
NEXThaler**

Changes in FEV1%





BUD/FORM
Turbuhaler

Adherence and Asthma Medication Ratio

Original Article

Assessment of Adherence and Asthma Medication Ratio for a Once-Daily and Twice-Daily Inhaled Corticosteroid/Long-Acting β -Agonist for Asthma

Richard H. Stanford, PharmD, MS^a, Carlyne Averell, MS, SM^a, Emily D. Parker, PhD, MPH^b, Cori Blauer-Peterson

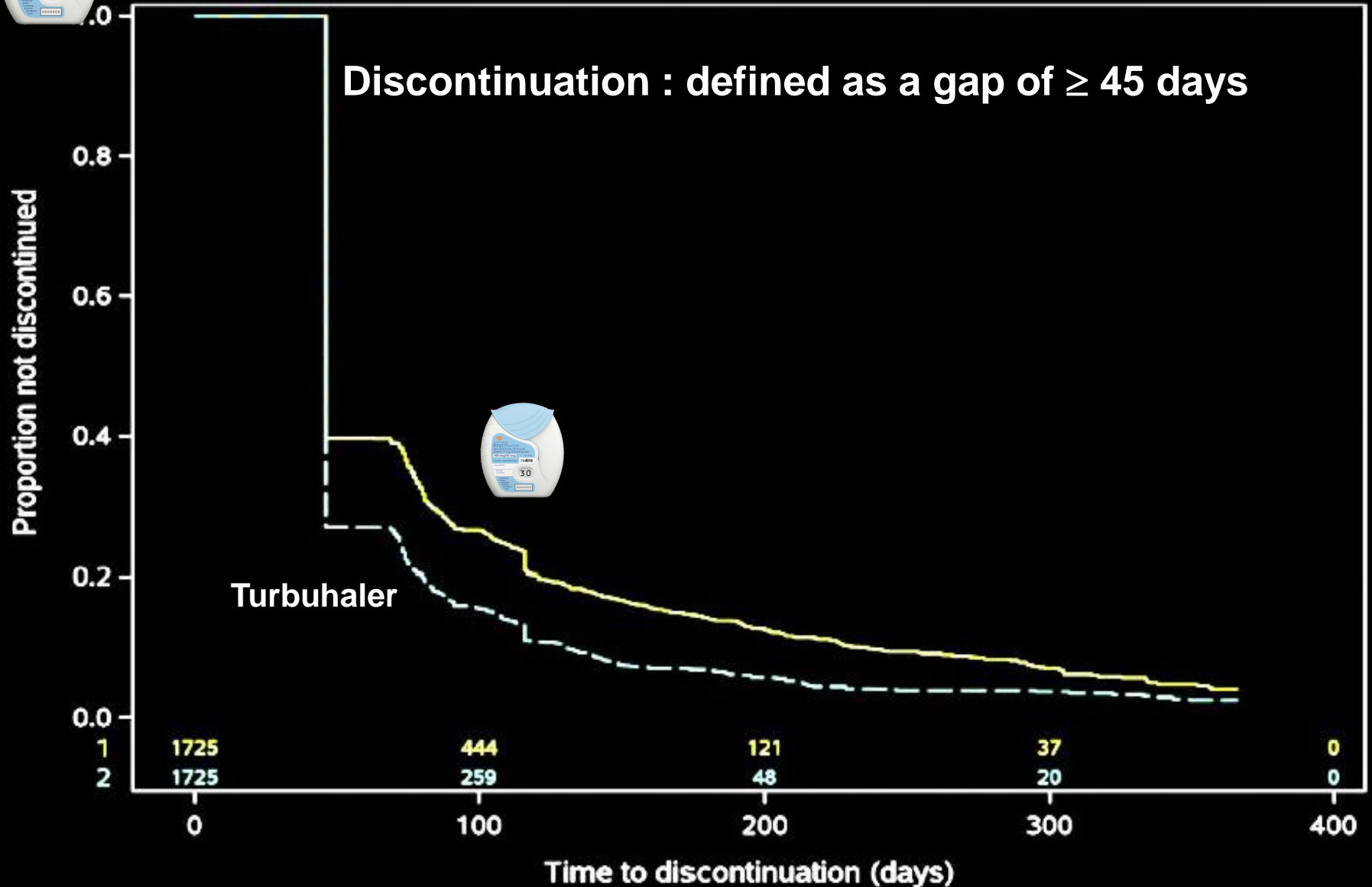
Retrospective, N = 9951. Propensity-score matching

$$\text{AMR} = \frac{\text{Controller medication use}}{\text{Total asthma medication}}$$



**BUD/FORM
Turbuhaler**

% Not Discontinued



Adherence and Asthma Medication Ratio (AMR)



Turbuhaler

	FF/VI 100/25µg n= 1,725	BUD/F 160/4.5µg n=1,725	p-value
Proportion of Days Covered (PDC), mean (SD)	0.43 (0.30)	0.36 (0.27)	<0.001
≥ 0.5, %	38.3	26.6	<0.001
≥ 0.8, %	17.5	10.2	<0.001
Treatment Discontinuation (within 12 months), %	88.4	93.2	<0.001
Asthma Medication Ratio (AMR), mean (SD)	0.63 (0.40)	0.57 (0.42)	<0.001
≥ 0.5, %	68.6	62.3	<0.001

	Adjusted OR	95% CI	P value
AMR > 0.5	1.36	1.23-1.50	<.001

AMR ≥ 0.5 :

- Lower risk of future asthma-related ED/IP visits
- Better patient-reported control and QoL outcomes

Cost-effectiveness ?

Current Price for ICS and ICS/LABA Inhalers in Taiwan

Tradename	Price
ICS	
FLIXOTIDE EVOHALER 50 MCG	200
PULMICORT TURBUHALER 200 MCG /DOSE 200 dose	366
ALVESCO 160	448
ICS/LABA	
SYMBICORT TURBUHALER 160/4.5UG/	1023
SYMBICORT RAPIHALER 160/4.5UG	1023
SERETIDE 50 EVOHALER	647
SERETIDE 125 EVOHALER	835
SERETIDE 250 EVOHALER	1109
RELVAR ELLIPTA 92/22 MCG	826
SERETIDE 50/500 ACCUHALER	1109
SERETIDE 250 ACCUHALER	835
SERETIDE 100 ACCUHALER	647
FOSTER/Nexhaler	758

Summary: Role of FF/VI in asthma

- Long-lasting molecules, >24 h



- Once-daily dosing



- Easy-to-use



1. Relvar Ellipta SmPC, 2018. 2. Bardsley G *et al. Resp Res* 2018; doi 10.1186/s12931-018-0836-6. 3. Braithwaite I *et al. Respir Med* 2016; 119:115–121. 4. Svedsater H *et al. NPJ Prim Care Respir Med* 2014; 24:14019. 5. Sharma R *et al. Am J Respir Crit Care Med* 2014; 189:A5693. 6. van der Palen J *et al. NPJ Prim Care Respir Med* 2016; 26:16079.

NO ideal inhaler for every patient



“ Inhaler phenotyping ”

Different inhalation techniques with different inhalers¹

Aerosol			DPI		
MDI	Soft mist inhaler	Breath-actuated pMDI	Single dose DPI – blister	Single dose DPI – capsule	Reservoir multidose DPI
pMDI	Respimat®	Autohaler®	Diskus®	Aerolizer®	Easyhaler®
		Easi-breathe®	Ellipta®	Breezhaler®	Genuair®
				HandiHaler®	NEXThaler®
					Turbohaler®

Slow inhalation needed

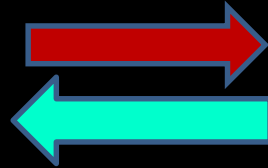
Forceful inhalation needed

1. Haidl P, et al. Respir Med 2016; 118: 65–75.

Simplified regimen for asthma in the near future ?




FF/VI



FF,VI/UM

Thank You !



Stepwise treatment to achieve total asthma control case sharing

中國醫藥大學附設醫院 胸腔暨重症系 陳家弘

Chen, Chia-Hung, MD-PhD

Assistant Professor, China Medical University

Department of Pulmonary and Critical Care Medicine

China Medical University Hospital

2019-06-23



IMAGE

ASTHMA AWARENESS



Case 1

Stepwise treatment to achieve total asthma control

Wheezing
dyspnea for 7 days

33 y/o, Male,
Asthma for 1 years under
Foster treatment at LMD

Visit our CHEST OPD for
further evaluation

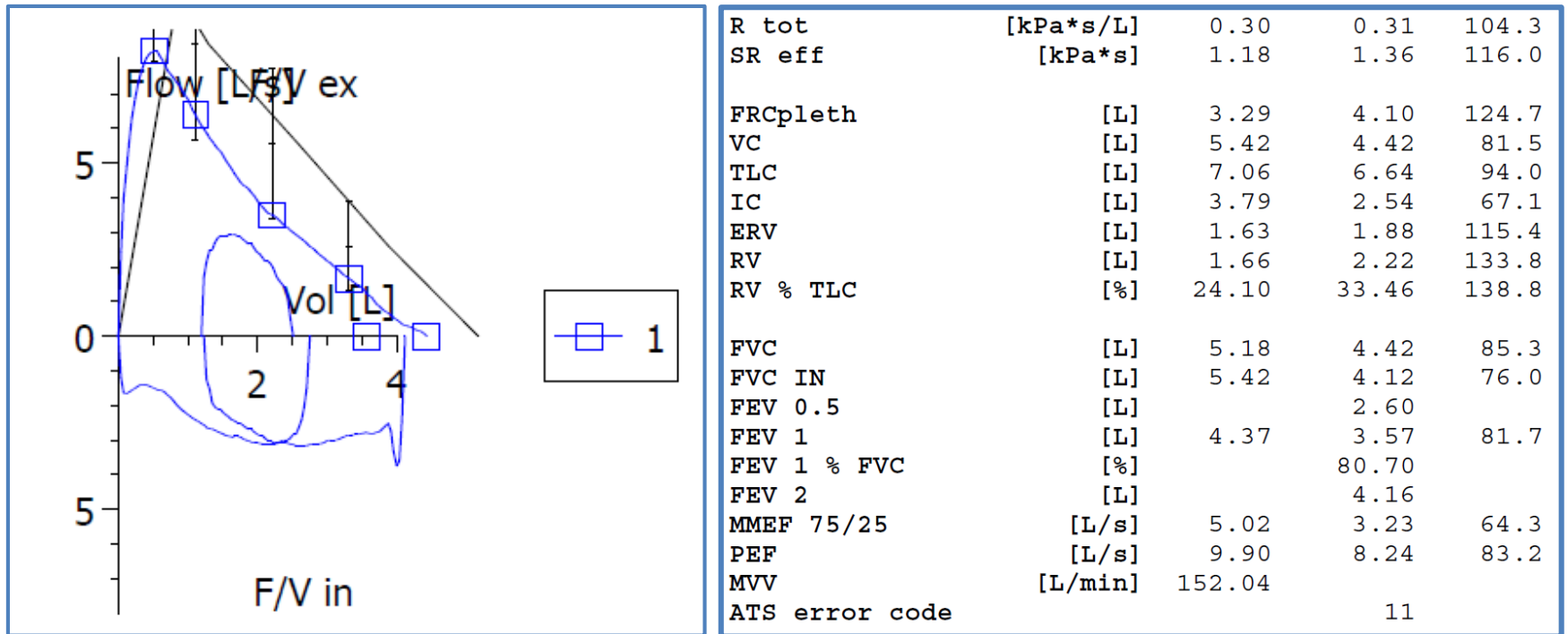
Case 1

2018/01/09 CxR

pt R

2018/01/09
14 04 55.03
25111

20180109 PFT



FEV1/FVC(Pred): **80.7%(75.9%)** ;

FEV1(%P): **3.57L(81.7%)** ; MMEF/Pred:64.3%

Laboratory-20180109

檢驗項目	報告內容	
WBC	10.2	x10 ³ /ul
Hb	15.8	g/dL
Platelet	186	x10 ³ /ul
Diff. Count		
Neutrophilic Segment	69.1	%
Lymphocytes	18.3	%
Monocytes	6.0	%
Eosinophils	3.4	%
Basophils	1.1	%

- **Eosinophil Count: 400 /ul**
- Phadiatop 吸入性過敏原篩檢試驗: **Positive** (冷光讀值: 3.962)
- ECP嗜伊紅球陽離子蛋白試驗: 4.63 ng/mL (<24)
- **IgE: 356.78 *** IU/mL (<165)

MAST Allergen Test

檢驗項目	報告值	等級
Avocado 酪梨	13 LU	class: 0
Pork 豬肉	7 LU	class: 0
Beef 牛肉	0 LU	class: 0
Cheddar cheese 起士	0 LU	class: 0
Clam 蚌殼類	7 LU	class: 0
Tuna 鮪魚	3 LU	class: 0
Soyabean 黃豆	6 LU	class: 0
Wheat(Food) 小麥	3 LU	class: 0
Brewer' s Yeast 啤酒酵母	6 LU	class: 0
Chicken Feathers 雞毛	9 LU	class: 0
Willow,Black 黑柳	13 LU	class: 0
Eucalyptus 尤加利	6 LU	class: 0
White Mulberry 白桑	12 LU	class: 0
Pigweed 莧科	3 LU	class: 0
Ragweed Mix I 豚草混合	4 LU	class: 0
Timoty Grass 牧草	0 LU	class: 0
Cladosporium 芽枝菌屬	7 LU	class: 0
Latex 乳膠	4 LU	class: 0

檢驗項目	報告值	等級
Housedust 家塵	19 LU	class: 0
Cockroach Mix 蟑螂混合	133 LU	class: 2
Mite DF 美洲塵蟎	213 LU	class: 2
Mite DP 歐洲塵蟎	150 LU	class: 1
Bermuda grass 狗牙根草	19 LU	class: 0
Japenses cedar 日本杉	8 LU	class: 0
Aspergillus 煙角麴菌	6 LU	class: 0
Alternaria tenuis 交錯黴菌	14 LU	class: 0
Penicillium 青黴菌	6 LU	class: 0
Cat dander 貓毛	12 LU	class: 0
Dog dander 狗毛	14 LU	class: 0
Egg white 蛋白	11 LU	class: 0
Milk 牛奶	0 LU	class: 0
Fish 鱈魚	5 LU	class: 0
Peanut 花生	10 LU	class: 0
Crab 蟹	21 LU	class: 0
Shrimp 蝦	9 LU	class: 0
Egg yolk 蛋黃	4 LU	class: 0

Patient characteristics

- 電路板技
術員

Occupation

- 媽媽

Family asthma
history

- none

Smoking

- None

Pet

- BH: 173 cm
- BW: 74 kg
- BMI: 24.3

BMI

- 20180109 Bronchial asthma Step 3
- Prescribed symbicort turbuhaler + Berotec
- ACT:3+3+3+2+3=14

- 20180402
- ACT:4+4+4+3+4=19
- Prescribed symbicort turbuhaler + Berotec

一週3次

一天2次

- 20180220
- ACT:4+4+4+2+4=18
- Prescribed symbicort turbuhaler + Berotec

- 20180509
- ACT:5+5+4+3+4=21

在過去四週中，您多常使用急救型藥物或噴霧型藥物 (例如: Albuterol*(舒坦寧*)、Ventolin*(泛得林*)、Berotec*(備勞喘*)或Bricanyl*(撲可喘*)等氣喘藥物)?

- | | | | | |
|----------------|-------------|-------------|--------------|--------------|
| 1
一天3次或3次以上 | 2
一天1或2次 | 3
一週2或3次 | 4
一週1次或更少 | 5
完全沒有使用過 |
|----------------|-------------|-------------|--------------|--------------|

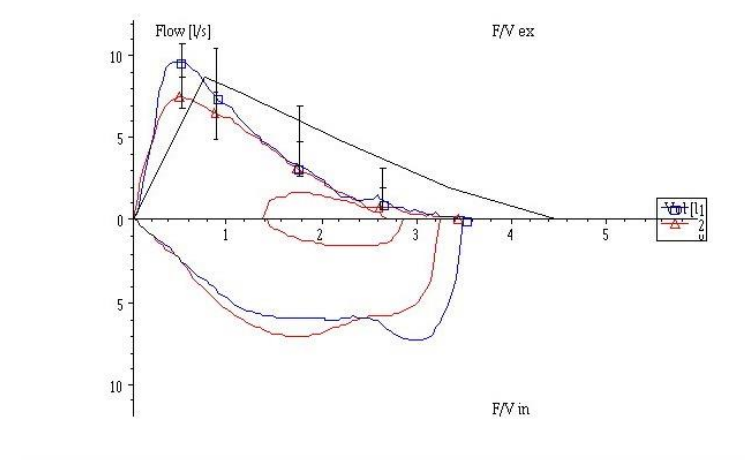
20180509 PFT

R tot.....[kPa*s/l]	0.30		0.34	113.7	
SR eff.....[kPa*s]	1.18		1.56	132.6	
ITGV.....[l]	3.54		4.12	116.4	
VC.....[l]	4.64		3.44	74.3	
TLC.....[l]	7.06		6.86	97.2	
ERV.....[l]	1.26		0.70	55.2	
RV.....[l]	2.28		3.42	150.2	
RV % TLC.....[%]	35.02		49.84	142.3	
FVC.....[l]	4.45	3.52	79.1	3.44	77.3
FVC IN.....[l]	4.64	3.45	74.3	3.20	69.0
FEV 0.5.....[l]		2.24		2.24	
FEV 1.....[l]	3.56	2.82	79.4	2.64	74.2
FEV 1 % FVC.....[%]		80.12		76.58	
FEV 2.....[l]		3.17		3.08	
MMEF 75/25.....[l/s]	3.81	2.28	59.7	2.13	56.0
PEF.....[l/s]	8.70	9.55	109.8	7.45	85.6

INTERPRETATION:

*Spirometry demonstrates early obstructive ventilatory

defect. FEV1/FVC(Pred):80.1%(72%); FEV1(%P):2.82L(79.4%); MMEF/Pred:59.7%



- FEV1/FVC: **80.1%**
- FEV1: **3.17L (79.4%)**

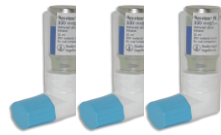
20180109-0509

120天

3罐 Symbicort



3罐 Berotec



ACT: 14->18->19->21

PFT: 3.57L-> 3.17L

What is your **next step** for persistent asthma despite of receiving **medium-dose ICS/LABA**?

To continue the current medications and improve patient-drug adherence

Add-on systemic treatments (e.g. systemic steroids, LTA..)

Step 5 Tx (e.g. tiotropium, Xolair, anti-IL5 mAb)

Shift to once daily ICS/LABA (e.g. Relvar)



SMART

Stepwise treatment to achieve total asthma control

Uncontrolled asthma

Fixed dose ICS/LABA

Variable dose ICS/LABA

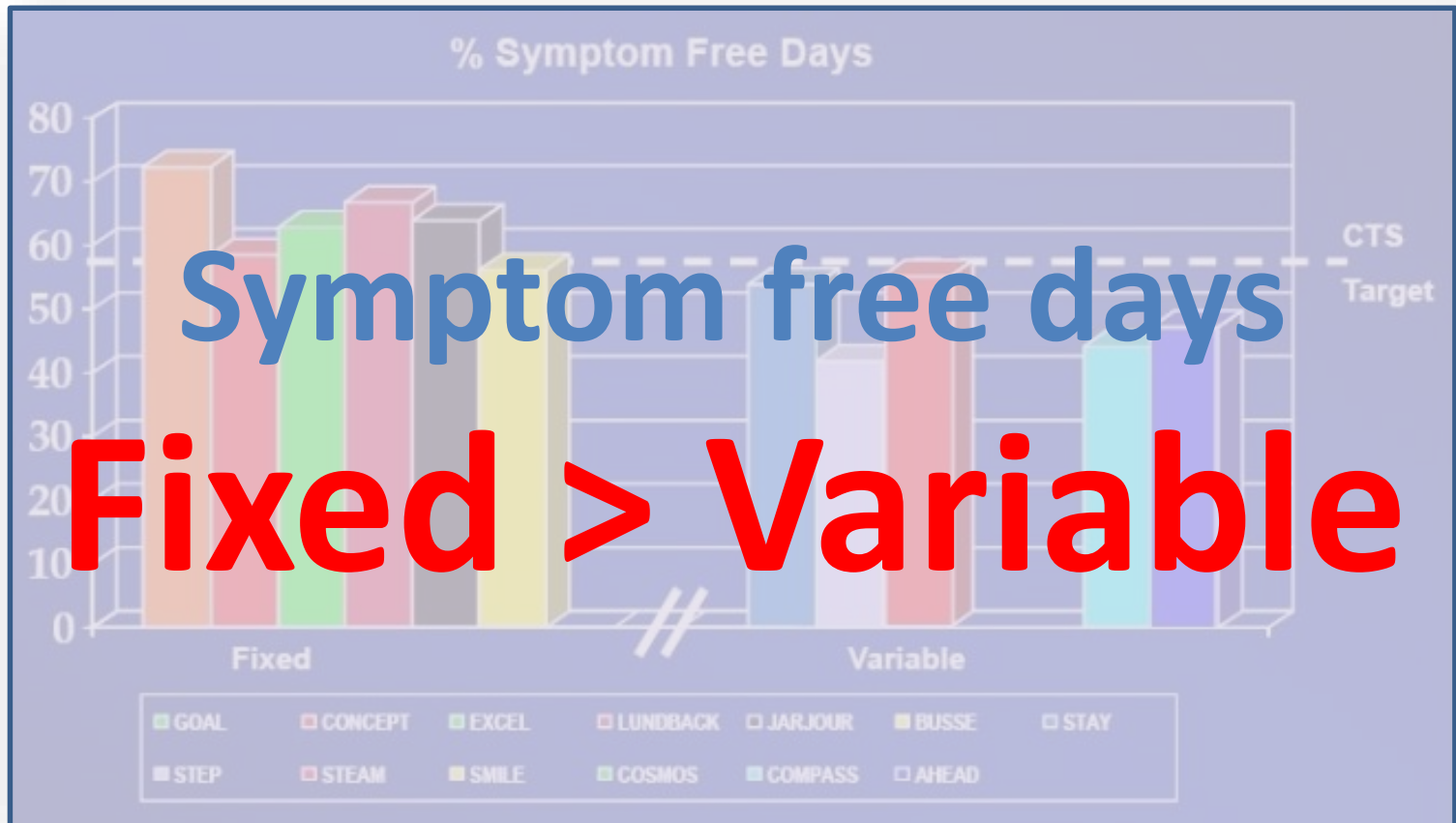
GOAL ¹	CONCEPT ²	EXCEL ³
LUNDBACK ⁴	JARJOUR ⁵	BUSSE ⁶

STAY ¹	STEP ²	SMILE ³
STEAM ⁴	COMPASS ⁵	AHEAD ⁶

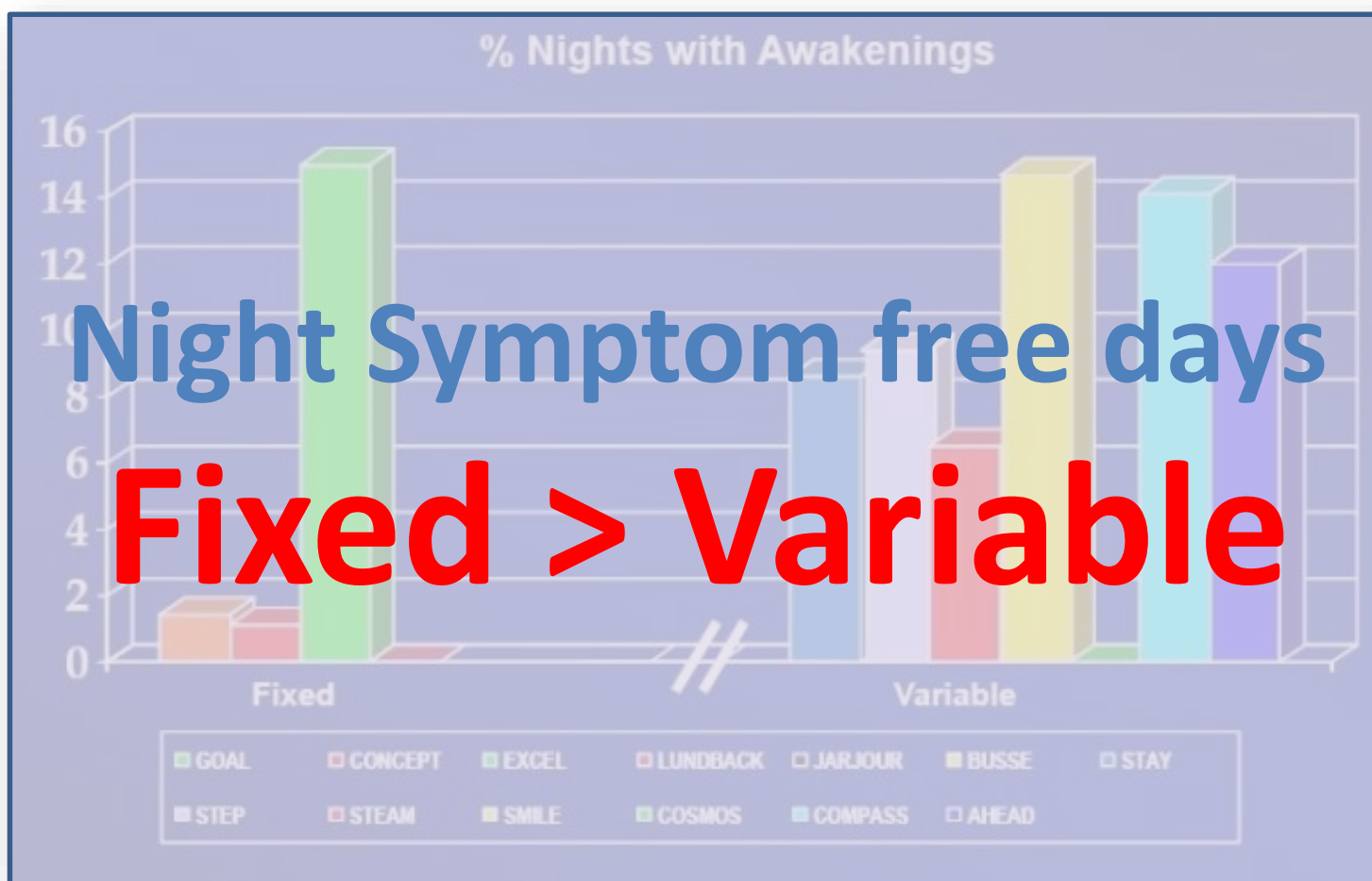
1. Bateman et al. *AJRCCM*. 2004;170:836–44
2. Clinical Therapeutics Volume 27, Number 4, 2005
3. Dahl et al. *Resp Medicine* 2006; 100:1152-1162
4. Bateman, et al. *JACI*. 2006;117(3):563–70
5. Antonicelli L et al. *Eur Respir J* 2004; 23: 723–729.
6. Bousquet J, et al. Abstract presented at ERS 2007

1. O'Byrne PM, et al. *AJRCCM*. 2005;171:129–36
2. Scicchitano R, et al. *Curr Med Res Opin*. 2004;20:1403–18
3. Rabe KF, et al. *Lancet*. 2006;368:744–53
4. Rabe KF, et al. *Chest*. 2006;129:246–56
5. Kuna P, et al. *Int J Clin Pract*. 2007;61:725–36
6. Bousquet J, et al. Abstract presented at ERS 2007

Asthma control: Fixed vs. Variable



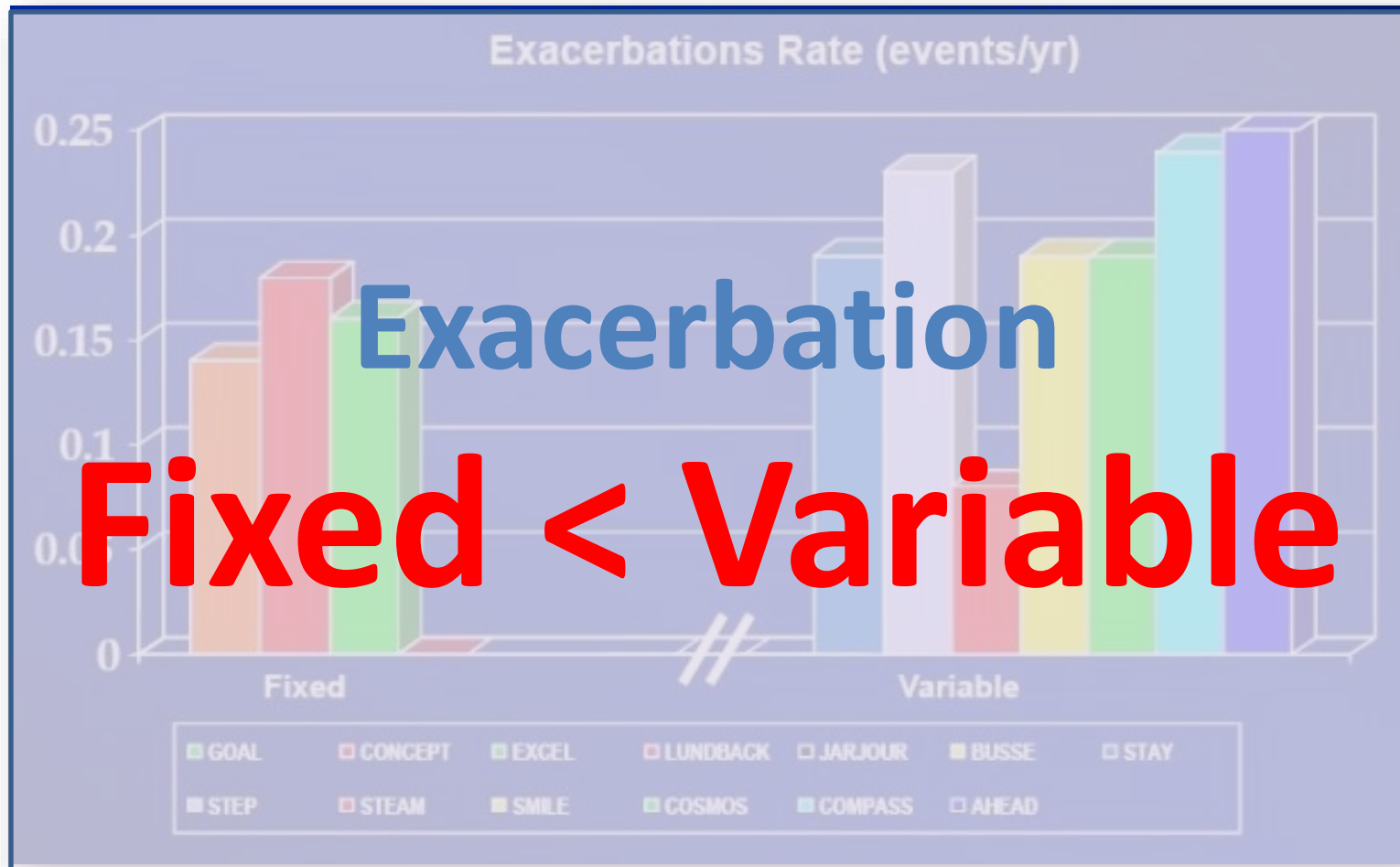
Asthma control: Fixed vs. Variable



Asthma control: Fixed vs. Variable



Asthma control: Fixed vs. Variable



“

SMART

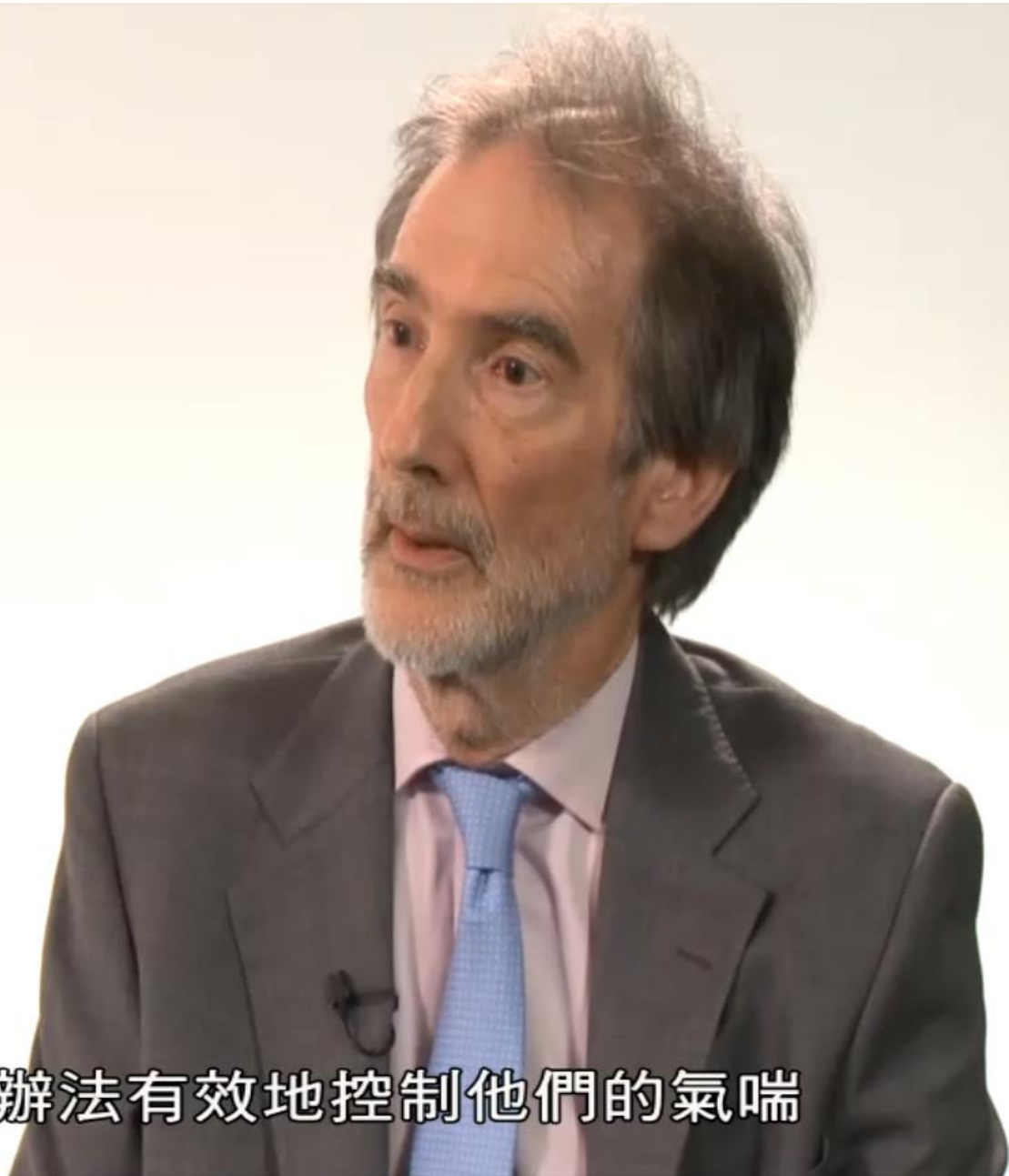
— 沒辦法 —

有效地
控制

— 他們的 —

氣喘

”



SMART沒辦法有效地控制他們的氣喘

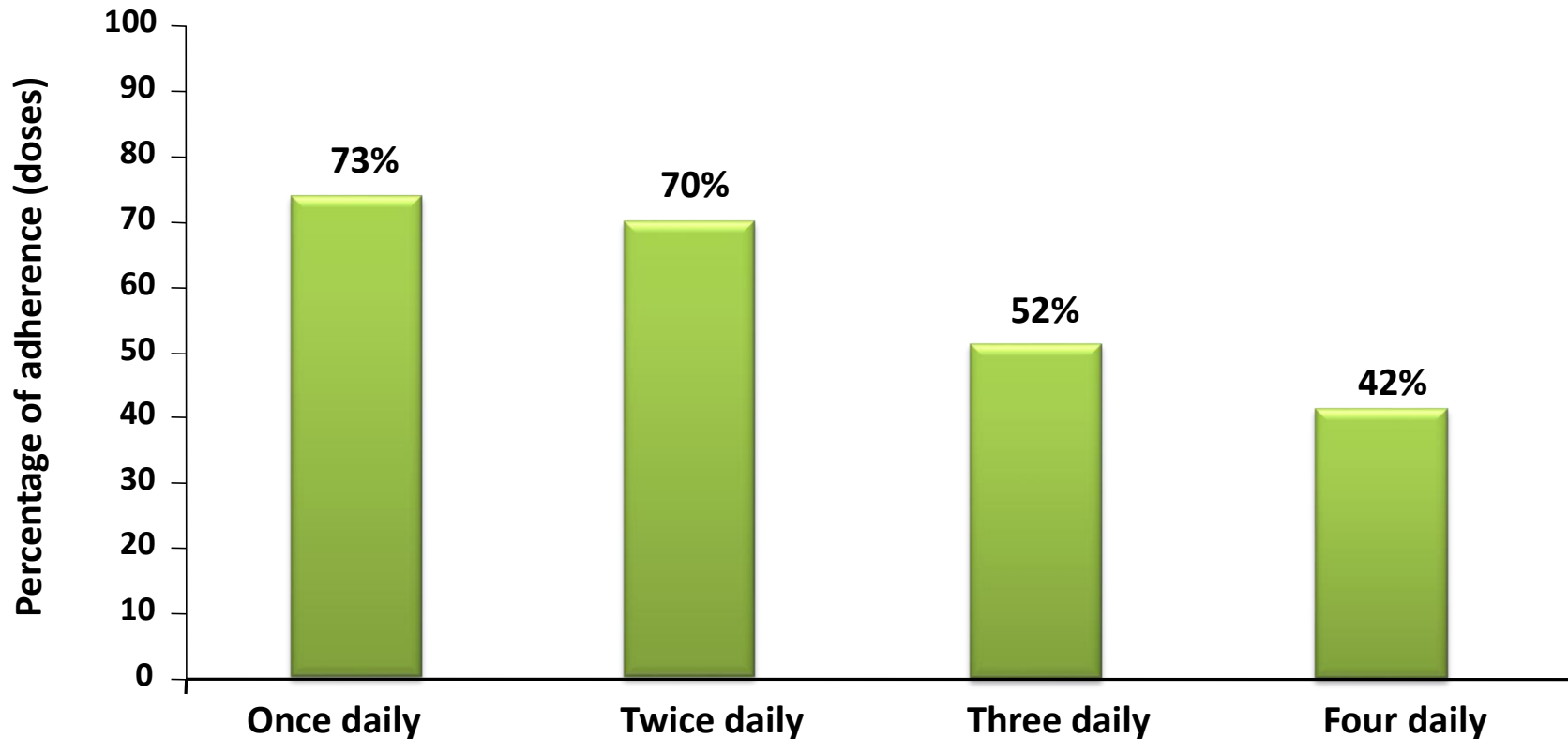


Once daily & Twice daily

Stepwise treatment to achieve total
asthma control

Dosing frequency and adherence

Literature review of 57 publications (all treatments – in 1981)



Impact of interval between doses

- Loss of effect with short half life
- Significance of missed dose

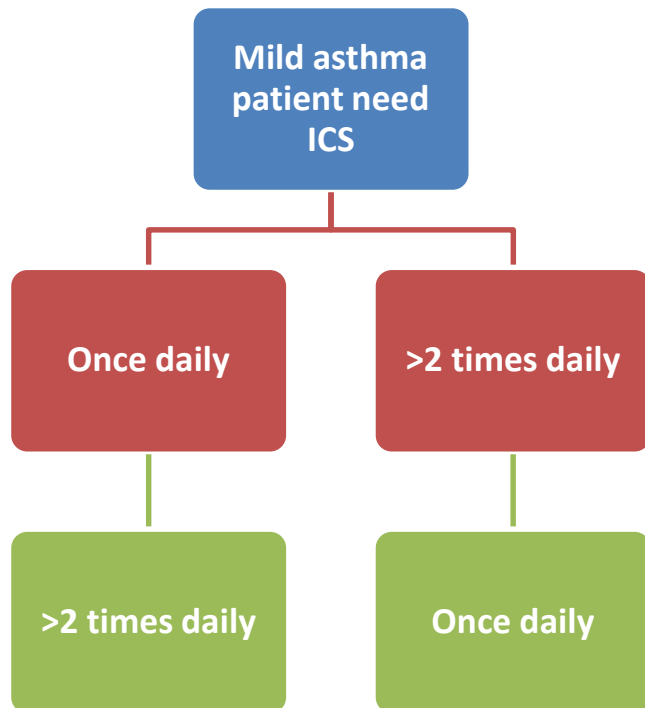
Greenberg RN. *Clin Ther* 1984;6:592-9.

Keen PJ. *J R Soc Med* 1991;84:640-1.

Real-world effects of once vs greater daily inhaled corticosteroid dosing on medication adherence

Karen E. Wells, MPH^{*}; Edward L. Peterson, PhD^{*}; Brian K. Ahmedani, PhD[†]; and L. Keoki Williams, MD, MPH^{†,‡}

Initial ICS dosing regimen	Initial adherence, mean (SD), %	Adherence after switch to alternate dosing regimen, mean (SD), % ^a	Difference in adherence after switch, mean (SD), % ^b	P value
Once daily (n = 62)	63.7 (32.1)	47.8 (30.2)	-15.9 (35.1)	.001
≥2 Times daily (n = 44)	48.1 (28.3)	74.4 (30.0)	26.3 (40.7)	.001



Once daily dosing was associated with an approximately 20% increase in adherence.

Once daily dosing was associated with higher adherence to ICS therapy



WORLD **ASTHMA** DAY

Conclusion

Stepwise treatment to achieve total asthma control

20180109-20180509

120天

3罐 Symbicort

3罐 Berotec

ACT: **14**->18->19->**21**

PFT: **3.57L**-> **3.17L**

Occupation

- 電路板技術員

上班48小時休息48
小時

Treatment

- Use symbicort smart for treatment

20180109-20180509

120天

3罐 Symbicort

3罐 Berotec

ACT: **14**->18->19->**21**

PFT: **3.57L**-> **3.17L**

- 不add-on tiotropium, 因為病人比較像**Th2 inflammation**
- 不step up 因為四個月只用三罐symbicort, 卻使用了3罐berotec, 代表**compliance**不佳

- 20180109 Bronchial asthma Step 3
- Prescribed symbicort turbuhaler + Berotec
- ACT:3+3+3+2+3=14

- 20180402
- ACT:4+4+4+3+4=19
- Prescribed symbicort turbuhaler + Berotec

- 20180530
- ACT:5+4+4+4+4=21
- Prescribed Relvar 100

- 20180220
- ACT:4+4+4+2+4=18
- Prescribed symbicort turbuhaler + Berotec

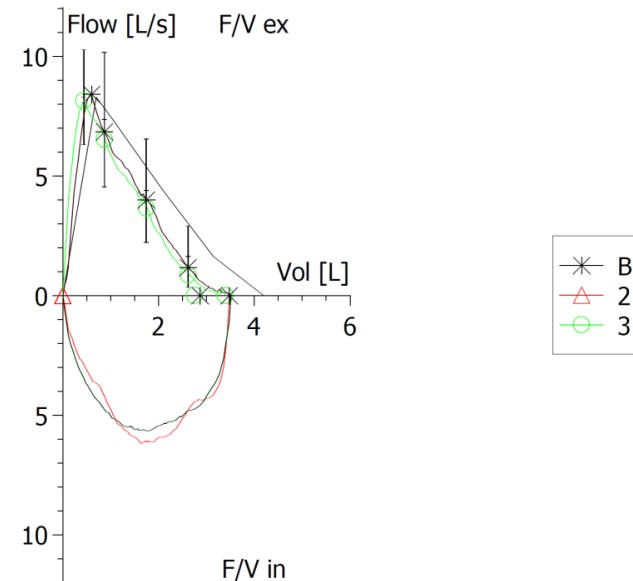
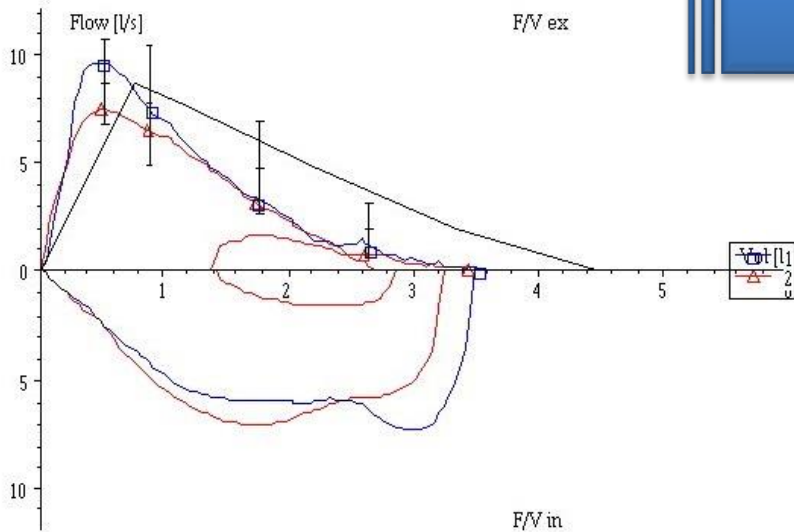
- 20180509
- ACT:5+5+4+3+4=21
- Prescribed Relvar 100

- 20180620
- ACT:5+5+5+4+4=23

20180509



20180826



- FEV1/FVC: **80.1%**
- FEV1: **3.17L (79.4%)**

- FEV1/FVC: **82.44%**
- FEV1: **3.88L (85.1%)**

IMAGE

ASTHMA AWARENESS



Case 2

Stepwise treatment to achieve total asthma control

A frontal chest X-ray (CXR) showing the lungs, heart, and spine. The lungs appear clear with no significant opacities. The heart size is within normal limits. The spine and ribs are visible. There are three white boxes with black text overlaid on the image, connected to the X-ray by lines. The top right box contains patient information. The middle left box contains symptoms. The middle right box contains a recommendation. The bottom left box contains the case number. The bottom center box contains the date and type of X-ray. The letters 'L' and 'R' are visible at the top right of the image, indicating the left and right sides of the patient.

Wheezing

dyspnea for 10 days
after exercise with GOLF

37 y/o, Male,
Asthma? Without
medicine

Visit our CHEST OPD for
further evaluation

Case 2

2018/03/01 CxR

Patient characteristics

- 中科機械工程師

Occupation

- 祖父

Family asthma history

- None

Smoking

- None

Pet

- BH: 170 cm
- BW: 69 kg
- BMI: 23.9

BMI

20180301 PFT

FVC.....[l]	4.19	3.46	82.4	3.59	85.6	3.8
FEV 0.5.....[l]		1.87		2.07		10.5
FEV 1.....[l]	3.36	2.41	71.5	2.61	77.6	8.5
FEV 1 % FVC.....[%]		69.61		72.76		4.5
FEV 2.....[l]		2.88		3.04		5.6
MMEF 75/25.....[l/s]	3.72	1.36	36.5	1.69	45.3	24.1
FEF 25.....[l/s]	7.38	3.85	52.2	5.02	68.0	30.3
FEF 50.....[l/s]	4.51	1.75	38.8	2.26	50.0	28.9
FEF 75.....[l/s]	1.76	0.50	28.2	0.63	35.8	27.0
PEF.....[l/s]	8.42	7.26	86.3	7.50	89.1	3.2

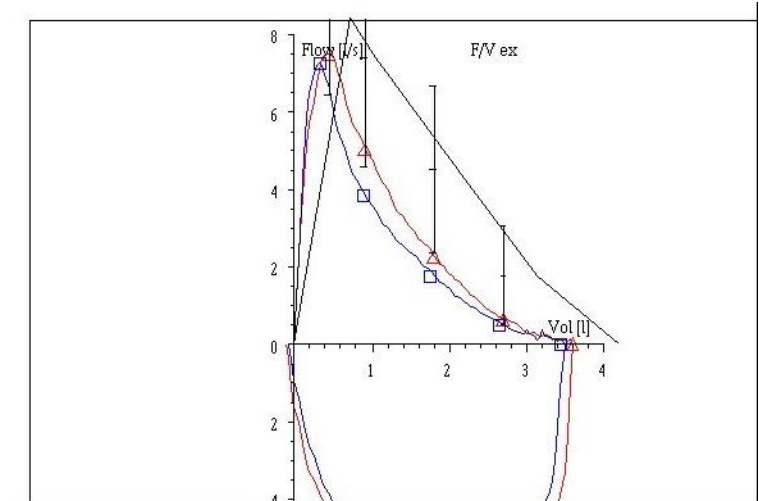
INTERPRETATION:

*Spirometry demonstrates mild obstructive ventilatory defect.

FEV1/FVC(Pred):69.91%(72.17%) ; FEV1(%P):2.41L(71.5%)

*Following the inhalation of a bronchodilator, there is no significant change in airway obstruction.

- FEV1/FVC: **69.91%**
- FEV1: **2.41L (71.5%)**



Laboratory-20180301

檢驗項目	報告內容	
WBC	9.94	x10 ³ /ul
Hb	14.2	g/dL
Platelet	313	x10 ³ /ul
Diff. Count		
Neutrophilic Segment	67.3	%
Lymphocytes	19.5	%
Monocytes	8.2	%
Eosinophils	4.7	%
Basophils	0.7	%

- **Eosinophil Count: 450 /ul**
- Phadiatop 吸入性過敏原篩檢試驗: **Positive** (冷光讀值: 3.962)
- ECP嗜伊紅球陽離子蛋白試驗: 11.3 ng/mL (<24)
- **IgE: 1091 *** IU/mL (<87)

MAST Allergen Test

檢驗項目	報告值	等級
Avocado 酪梨	13 LU	class: 0
Pork 豬肉	7 LU	class: 0
Beef 牛肉	0 LU	class: 0
Cheddar cheese 起士	0 LU	class: 0
Clam 蚌殼類	7 LU	class: 0
Tuna 鮭魚	3 LU	class: 0
Soyabean 黃豆	6 LU	class: 0
Wheat(Food) 小麥	3 LU	class: 0
Brewer' s Yeast 啤酒酵母	6 LU	class: 0
Chicken Feathers 雞毛	9 LU	class: 0
Willow,Black 黑柳	13 LU	class: 0
Eucalyptus 尤加利	6 LU	class: 0
White Mulberry 白桑	12 LU	class: 0
Pigweed 莧科	3 LU	class: 0
Ragweed Mix I 豚草混合	4 LU	class: 0
Timoty Grass 牧草	0 LU	class: 0
Cladosporium 芽枝菌屬	7 LU	class: 0
Latex 乳膠	4 LU	class: 0

檢驗項目	報告值	等級
Housedust 家塵	19 LU	class: 0
Cockroach Mix 蟑螂混合	33 LU	class: 1
Mite DF 美洲塵蟎	71 LU	class: 1
Mite DP 歐洲塵蟎	108 LU	class: 1
Bermuda grass 狗牙根草	214 LU	class: 3
Japenses cedar 日本杉	0 LU	class: 0
Aspergillus 煙角麴菌	0 LU	class: 0
Alternaria tenuis 交錯黴菌	0 LU	class: 0
Penicillium 青黴菌	2 LU	class: 0
Cat dander 貓毛	12 LU	class: 1
Dog dander 狗毛	14 LU	class: 0
Egg white 蛋白	11 LU	class: 0
Milk 牛奶	0 LU	class: 0
Fish 鱈魚	5 LU	class: 0
Peanut 花生	10 LU	class: 0
Crab 蟹	21 LU	class: 0
Shrimp 蝦	9 LU	class: 0
Egg yolk 蛋黃	4 LU	class: 0





一、狗牙根草 (*Cynodon dactylon*-Bermuda sp.)

狗牙根培育品種

天堂草 <i>Tifgreen</i>	短提福 <i>Tifdwarf</i>	老鷹草 <i>Tif Eagle</i>	冠軍百慕大 <i>Champion grass</i>
			

二、結縷草 (*Zoysia* sp.)

結縷草培育品種

日本結縷草 (<i>Zoysia japonica</i>)	馬尼拉結縷草 (<i>Zoysia matrella</i>)	細葉結縷草 (<i>Zoysia tenuifolia</i>)	“伊爾·葉蕾” 結縷草 (El Toro <i>Zoysia</i>)
			

三、雀稗草 (*Paspalum* sp.)

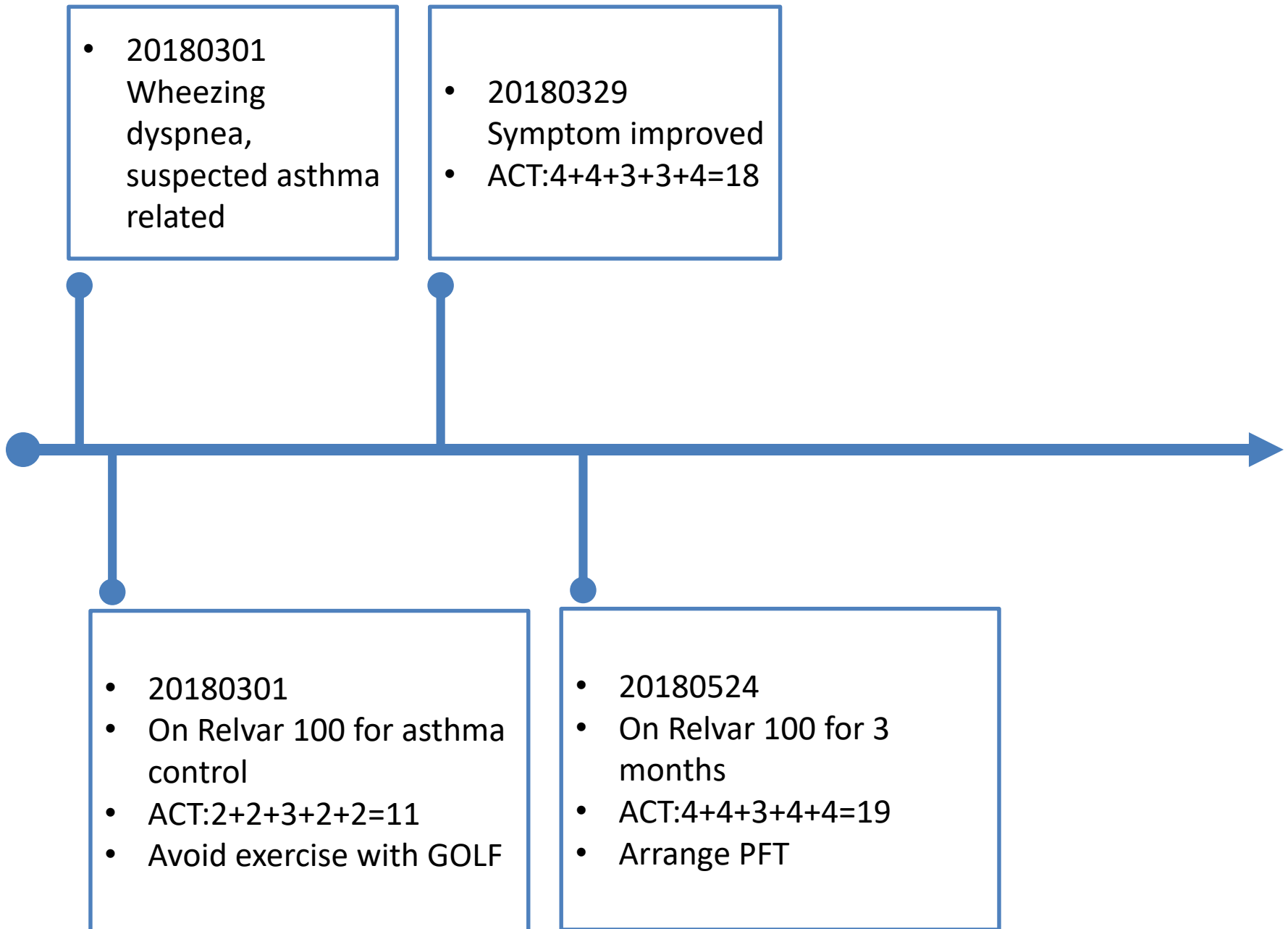
雀稗草培育品種

<i>Seashore Paspalum</i> Salam	<i>Seashore Paspalum</i> 2000	<i>Seashore Paspalum</i> Supreme	Platinum
			

四、地毯草 (*Axonopus* sp.)

地毯草培育品種

<i>Axonopus compressus</i>

- 20180301 Wheezing dyspnea, suspected asthma related

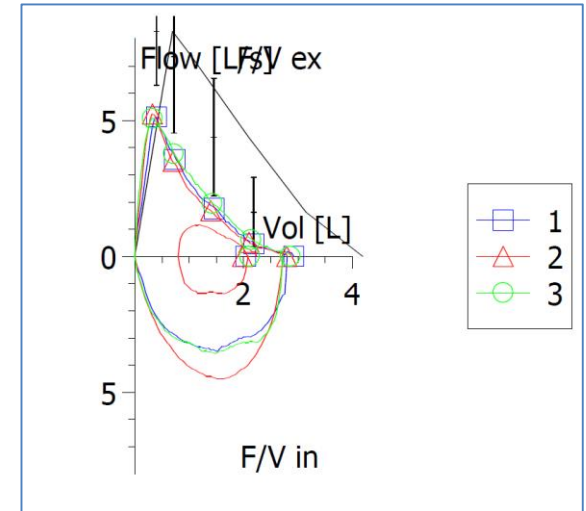
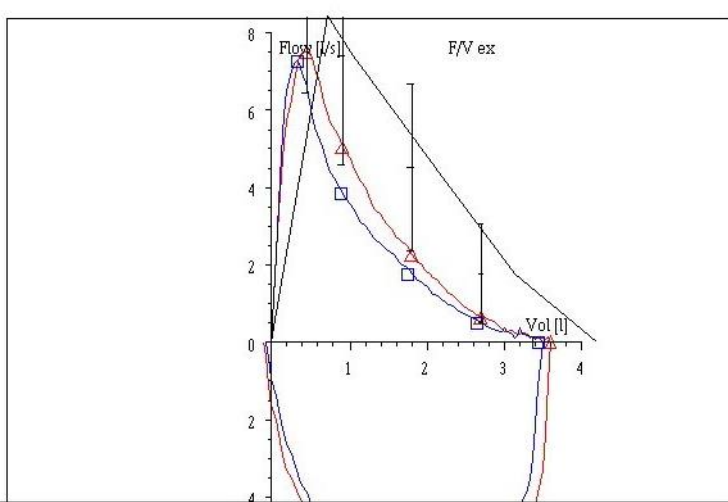
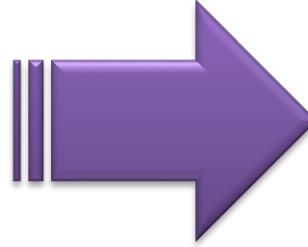
- 20180329 Symptom improved
- ACT:4+4+3+3+4=18

- 20180301
- On Relvar 100 for asthma control
- ACT:2+2+3+2+2=11
- Avoid exercise with GOLF

- 20180524
- On Relvar 100 for 3 months
- ACT:4+4+3+4+4=19
- Arrange PFT

20180301 PFT

20180524 PFT



- FEV1/FVC: **69.91%**
- FEV1: **2.41L (71.5%)**

- FEV1/FVC: **68.4%**
- FEV1: **2.33L (69.1%)**

What is your **next step** for persistent asthma despite of receiving **low-dose ICS/LABA**?

To continue the current medications and improve patient-drug adherence

Step up to high dose ICS/LABA

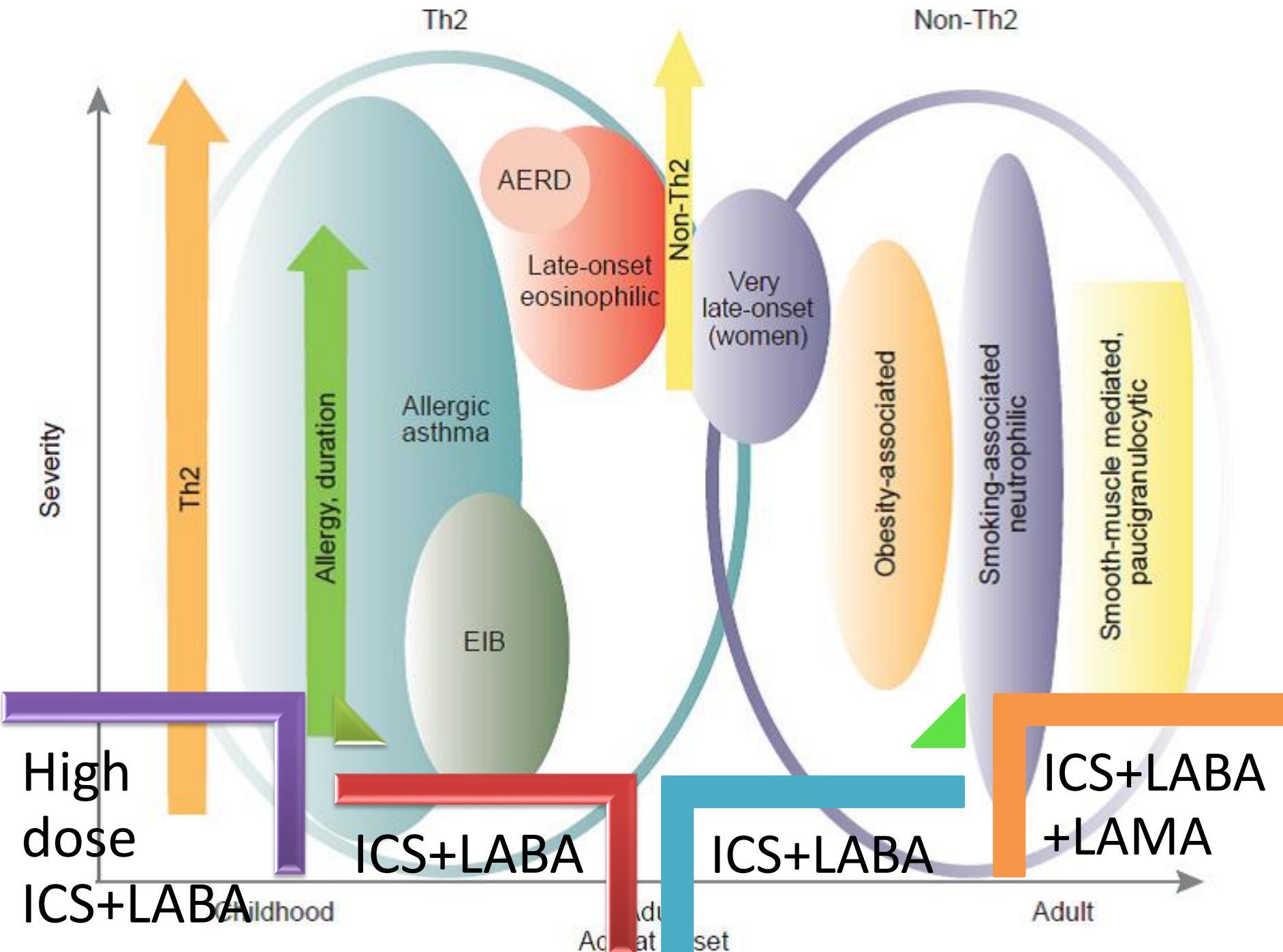
Add on tiotropium treatment

Add on biologic agent treatment



Phenotype therapy

Stepwise treatment to achieve total
asthma control



Different treatment in uncontrolled asthma



Uncontrolled asthma

- Maybe under use ICS
- High dose ICS improved severe asthma
- May consider as initial therapy with high dose ICS

High dose
ICS+LABA



TH2 inflammation

- Allergic asthma
- Exercise induced bronchoconstriction
- Aspirin related respiratory disease
- Late onset eosinophilic

ICS+LABA+
LAMA



Non-Th2 inflammation

- Very late onset female
- Obesity associated
- Smoking associated
- neutrophilic
- Paucigranulocytic
- Virus induced

Different treatment in uncontrolled asthma



Uncontrolled
asthma after
ICS+LABA

High dose
ICS+LABA



TH2 inflammation

High dose ICS
+LABA should be
used for uncontrolled
asthma

Non-Th2 inflammation

ICS+LABA+LAMA
should be used for
uncontrolled
asthma

ICS+LABA+
LAMA



High dose ICS/LABA VS low dose ICS/LABA

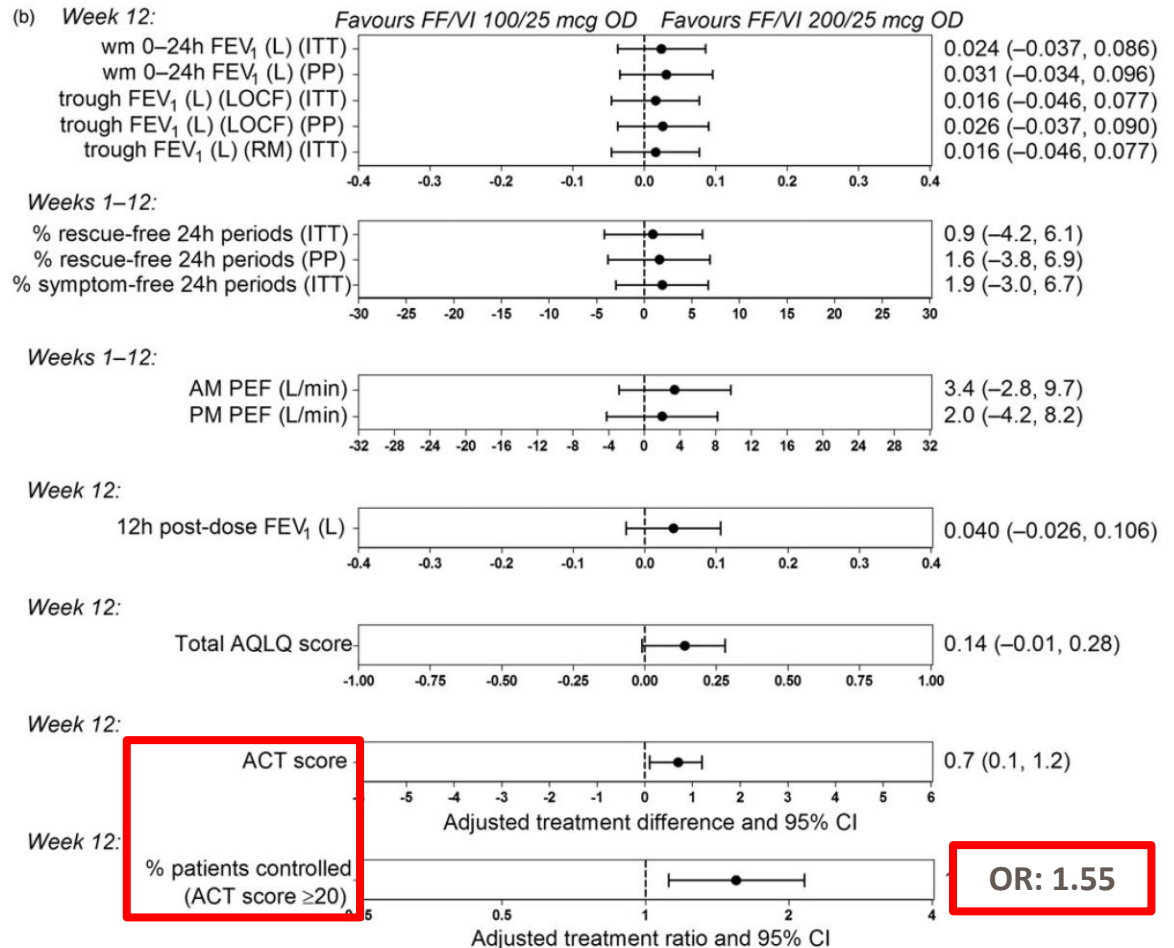
Stepwise treatment to achieve total
asthma control

Fluticasone furoate (FF)/vilanterol (100/25 mcg or 200/25 mcg) or FF (100 mcg) in persistent asthma

David I. Bernstein MD^a, Eric D. Bateman MD^b, Ashley Woodcock MD^c, William T. Toler PharmD, MBA^d, Richard Forth MMathStat^e, Loretta Jacques PhD^f, Carol Nunn MBBS^f & Paul M. O'Byrne MB^g

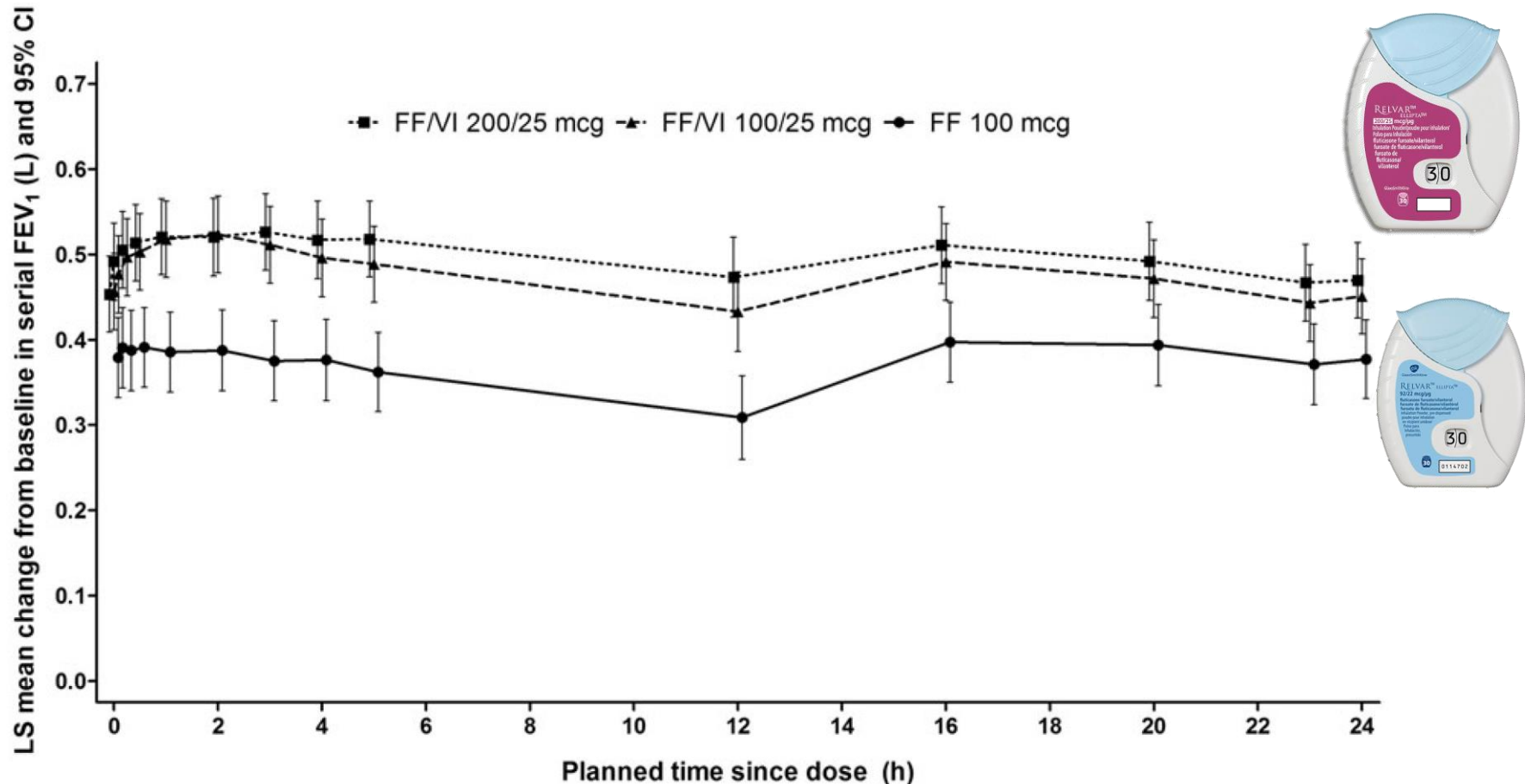
- age 12 years and moderate to severe asthma treated with an ICS±LABA for 12 weeks;
- Still uncontrolled

在Moderate to severe 氣喘病患上，Relvar 200可以比Relvar 100改善更多氣喘症狀



Fluticasone furoate (FF)/vilanterol (100/25 mcg or 200/25 mcg) or FF (100 mcg) in persistent asthma

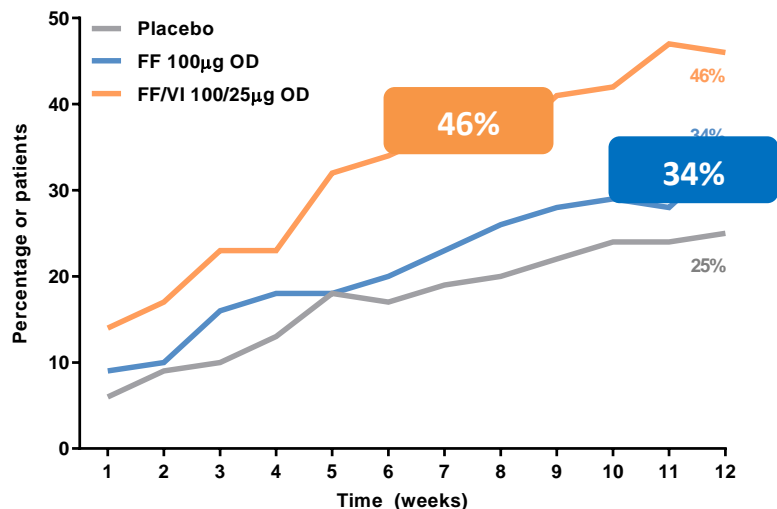
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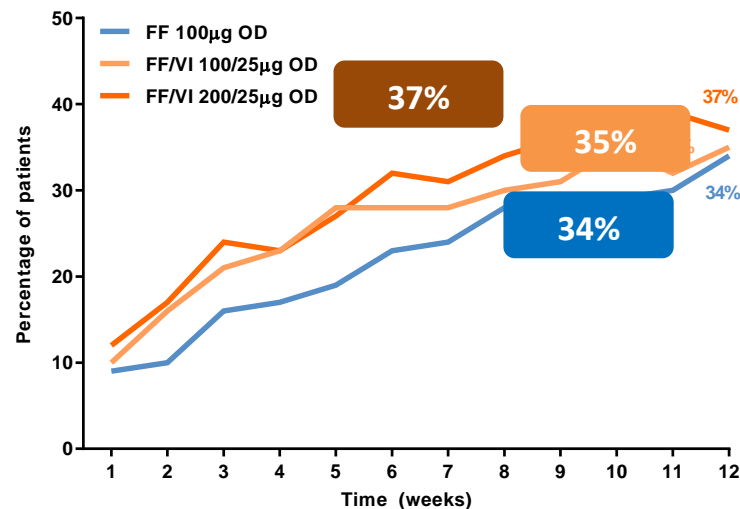
More patients achieved 100% symptom-free nights with FF/VI than with FF or FP alone.

Changes in night-time awakenings

Patients with mild/moderate asthma, uncontrolled on low/mid-dose ICS or low-dose ICS/LABA (Bleecker 2014)¹



Patients with moderate/severe asthma, uncontrolled on high-dose ICS or mid-dose ICS/LABA (Bernstein 2015)²



Bleecker ER, et al. *J Allergy Clin Immunol Pract* 2014;2:553–61;

Bernstein DI, et al. *J Asthma* 2015;52:1073–83.;

O'Byrne PM, et al. *Eur Respir J* 2014;43:773–82

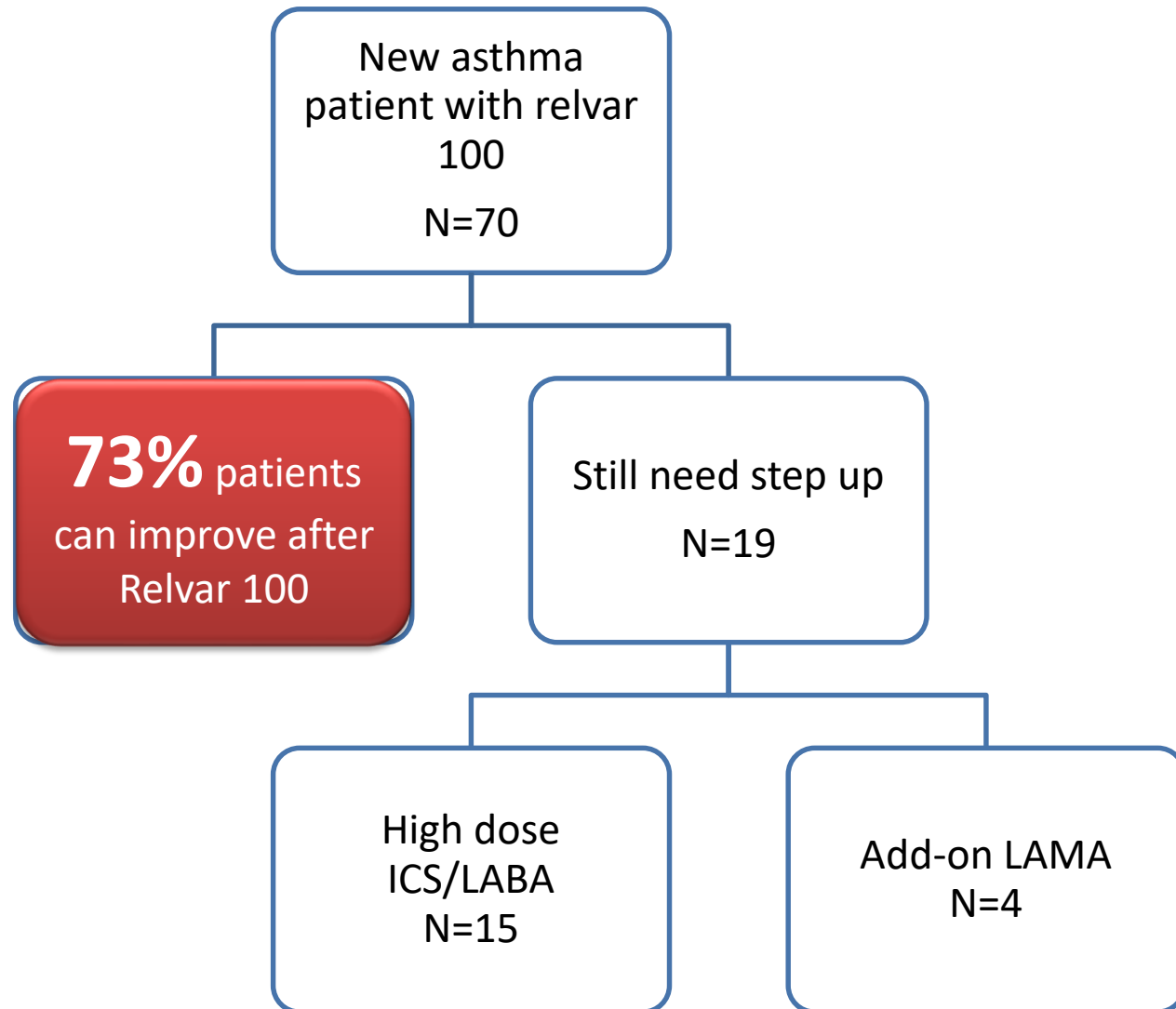


WORLD
ASTHMA
DAY

When to use high dose ICS/LABA

Stepwise treatment to achieve total
asthma control

New diagnosis asthma from 2017-01 to 2017-12 in CMUH



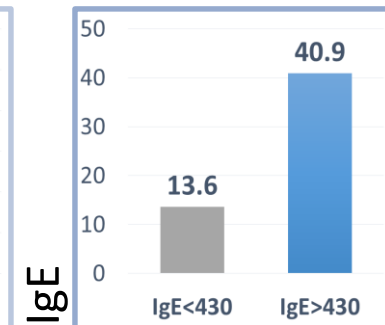
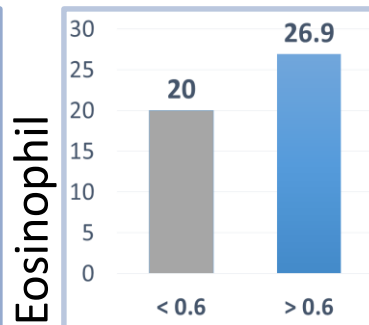
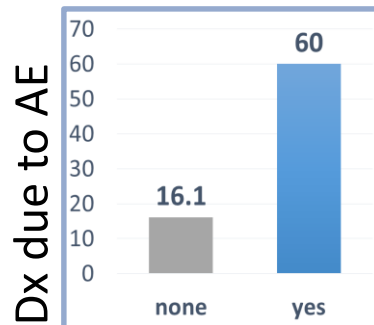
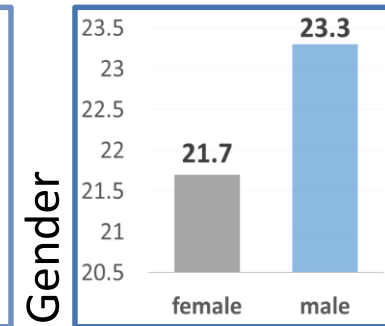
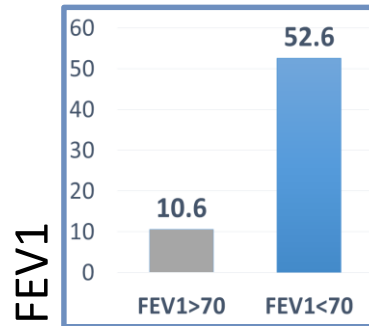
Factors affecting the need high dose ICS/LABA after Relvar 100



107/01-107/12
New diagnosis of
asthma
At CMUH

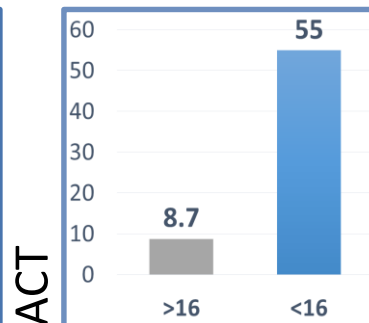
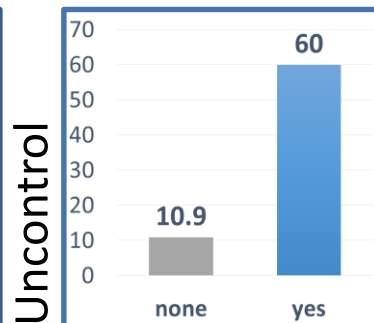
Relvar
n=51

High dose
ICS/LABA
n=15



P value

gender	0.889
FEV1	0.001
IgE	0.026
Eosinophil	0.558
AE	0.007
ACT	0.001
control	0.001



Need High dose ICS/LABA after Relvar

Multivariate analysis

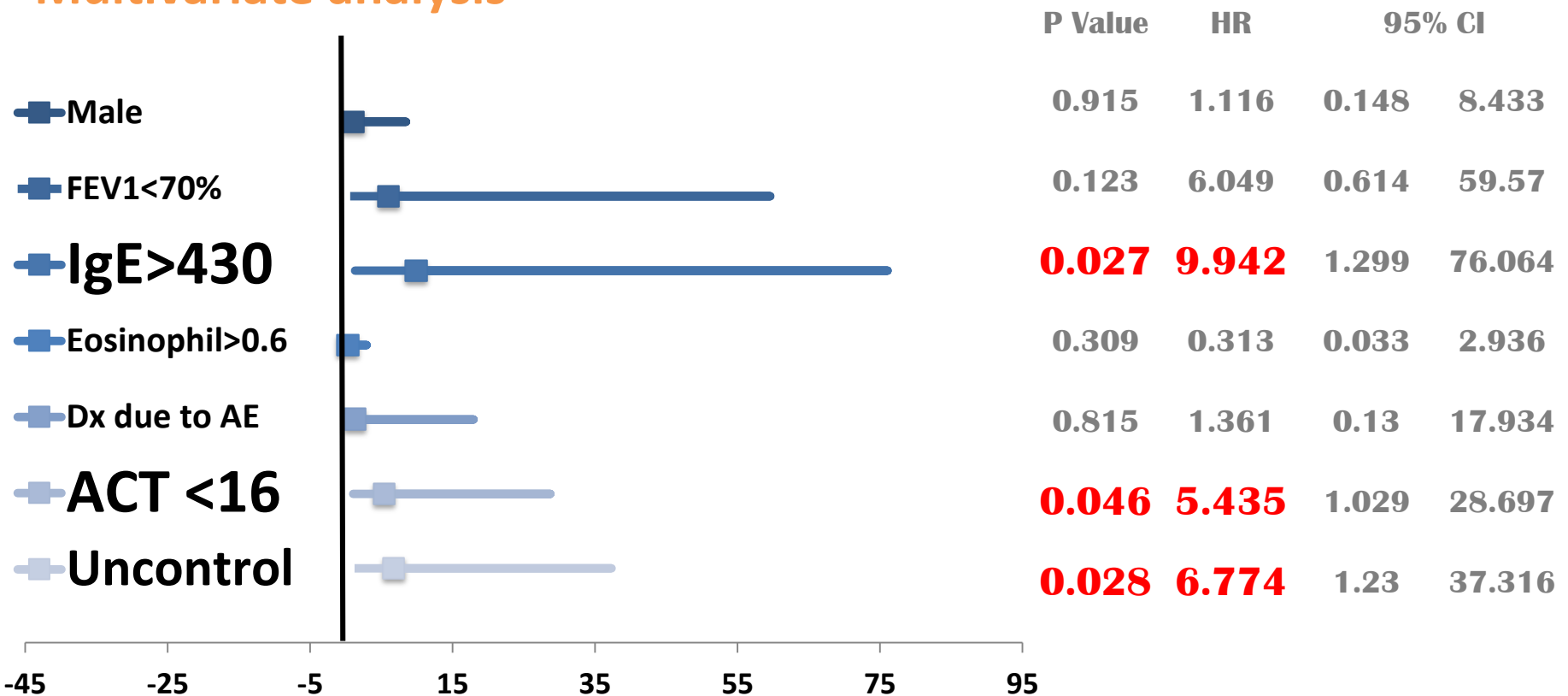


Table 1 Demographic characteristics, asthma status, and treatment at screening

Variables	HD group (n = 76)	GD group (n = 80)	P-value
Age	46.4 ± 20.3	48 ± 23.4	0.95
Gender (Male/female)	24/52	26/54	0.88
Atopy status	26 (34.2)	31 (38.6)	0.54
Control status			
Partly controlled (%)	38 (50)	41 (51.3)	0.91
Uncontrolled (%)	25 (32.9)	27 (33.7)	
Uncontrolled + AE (%)	13 (17.1)	12 (15)	
Asthma Control Test	16 ± 4	17 ± 5	0.72
Lung function			
FEV ₁ pre-salbutamol (L)	2.36 ± 0.57	2.34 ± 0.52	0.59
FEV ₁ post-salbutamol (L)	2.71 ± 0.81	2.72 ± 0.92	0.48
FEV ₁ % predicted	66.1 ± 10.3	68.4 ± 9.8	0.27
FEV ₁ reversibility (%)	25.6 ± 11.6	24.9 ± 10.1	0.42
Medications at baseline before R			
Fluticasone/salmeterol, 125/25 (%)	54 (71.1)	52 (65.0)	0.35
Fluticasone, 125 (%)	22 (28.9)	27 (35.0)	
Theophylline (%)	37 (48.9)	39 (48.6)	0.62
Leukotriene modifiers (%)	27 (35.5)	31 (38.7)	0.66
Initial medications after R			
Fluticasone/salmeterol, 250/25 (%)	65 (85.5)	22 (27.5)	<0.01*
Fluticasone/salmeterol, 125/25 (%)	11 (14.5)	53 (66.3)	
Fluticasone, 125 (%)	0 (0)	5 (6.2)	
Theophylline (%)	53 (69.7)	46 (57.5)	0.27
Leukotriene modifiers (%)	41 (53.9)	34 (42.5)	0.36

- Uncontrolled
- Low ACT
- Low FEV1

Need **High dose ICS**

Early achievement and maintenance of stable asthma control using initially higher-dose inhaled corticosteroids as part of combination therapy: an open-label pilot study

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy
14 June 2013
Number of times this article has been viewed

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Background: Uncontrolled asthma is characterized by considerable variability. Well controlled asthma is associated with less unplanned use of health care resources and fewer acute exacerbations. In this study, we attempted to increase inhaled corticosteroid (ICS) doses initially in suboptimally controlled asthmatics, hypothesizing that early achievement of asthma control using this strategy would be associated positively with a higher level of stability.

Methods: This was a randomized, open-label, prospective study including patients with uncontrolled asthma who were randomized to receive higher-dose (HD) ICS in combination with a long-acting beta-agonist (LABA) for one month and then shifted to doses suggested in the practice guidelines (GD) or to receive GD therapy alone. Lung function, ie, forced expiratory volume in one second (FEV₁), peak expiratory flow, Asthma Control Test scores, and frequency of acute exacerbations, was followed up for one year.

Results: Seventy-six patients were treated with the HD strategy and 80 with the GD strategy. The increase in FEV₁ from baseline was greater in the HD group than in the GD group, especially during the first month of treatment (304 ± 49 mL, versus 148 ± 39 mL, respectively, *P* = 0.01). Numbers of patients with completely or well controlled asthma were higher in the HD group than in the GD group (92.1% versus 81.1%, respectively, *P* = 0.03). Further, there was a significant difference between the groups with regard to frequency of acute exacerbations (9.2% in the HD group versus 21.3% in the GD group, *P* = 0.02); this effect was more pronounced for patients in the HD group with partially controlled or uncontrolled asthma.

Conclusion: Patients receiving HD therapy achieved asthma control more rapidly and maintained greater stability than those receiving GD therapy. This represents a novel strategy for gaining disease control in patients with uncontrolled asthma.

Keywords: asthma, treatment, inhaled corticosteroids, higher doses



WORLD **ASTHMA** DAY

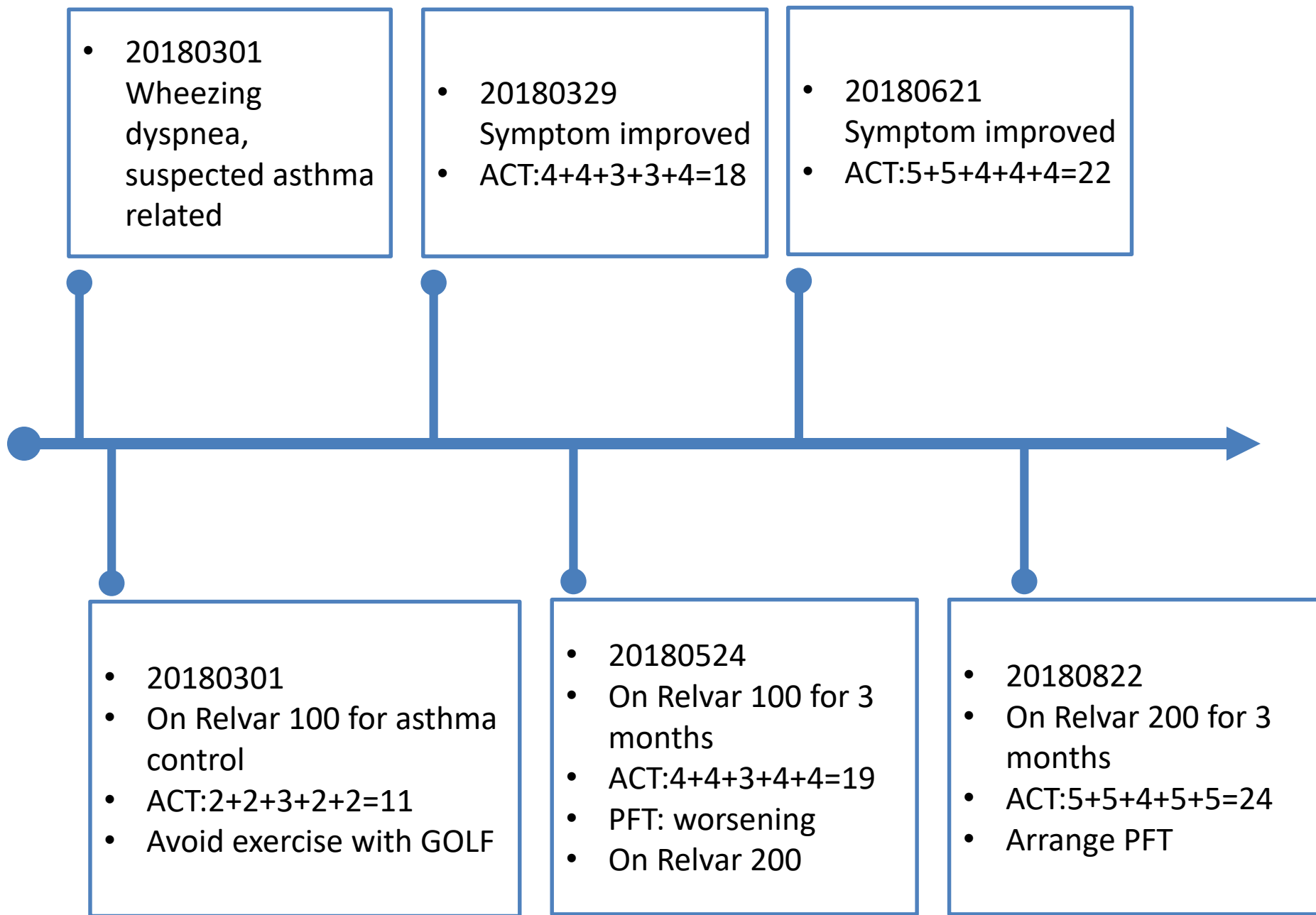
Conclusion

Stepwise treatment to achieve total asthma control

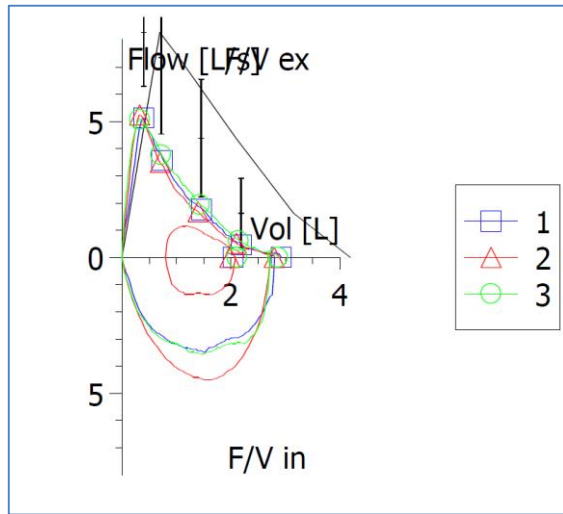
Next step in this patient



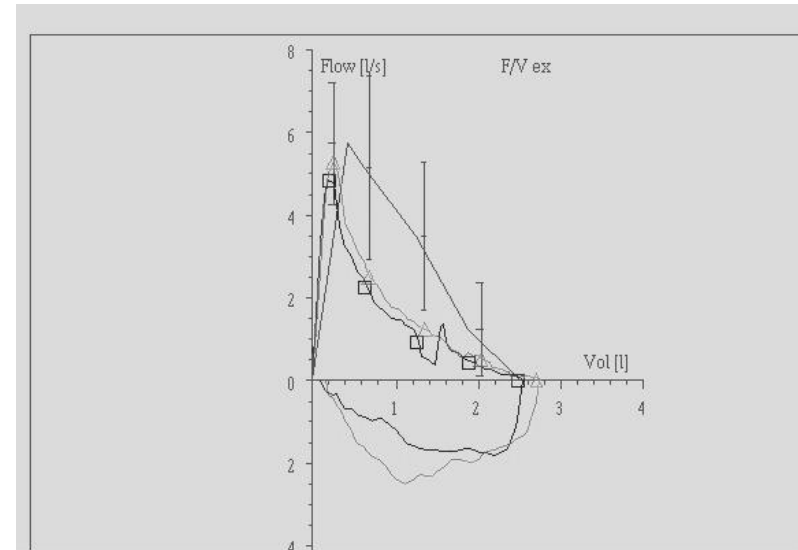
FeNO: **52** ppb



20180524 PFT



20180822 PFT



- FEV1/FVC: **68.4%**
- FEV1: **2.33L (69.1%)**

- FEV1/FVC: **66%**
- FEV1: **2.54L (75.3%)**



FeNO: **52** ppb



FeNO: **23** ppb

FeNO levels and inflammation

FeNO (ppb)*	LOW	INTERMEDIATE	HIGH
Adults	<25	25-50	>50

Monitoring (in patients with diagnosed asthma)

Symptoms present	<ul style="list-style-type: none"> Consider alternative diagnosis Not likely to respond to increased ICS dose Consider rechecking in 2-3 months 	<ul style="list-style-type: none"> Consider persistent allergen exposure Check adherence Consider increasing ICS dose Consider steroid resistance Consider rechecking in 2-3 months 	<ul style="list-style-type: none"> Consider persistent allergen exposure Check adherence and inhaler technique Consider increasing ICS dose Consider other anti-inflammatory therapy Consider rechecking in 2-4 weeks
Symptoms absent	<ul style="list-style-type: none"> Adequate ICS dose Good adherence If on ICS, consider decreasing dose or discontinuing ICS Consider rechecking in 2-4 weeks 	<ul style="list-style-type: none"> Adequate ICS dosing Good adherence Monitor change in FeNO Consider rechecking in 2-3 months 	<ul style="list-style-type: none"> ICS withdrawal or dose reduction may result in relapse Poor adherence or inhaler technique Consider rechecking in 2-3 months

FeNO **Low** Symptom **Absent**

- Adequate ICS dose
- Good adherence
- If on ICS, consider decreasing dose or discontinuing ICS

- 20180301 Wheezing dyspnea, suspected asthma related

- 20180524
- On Relvar 100 for 3 months
- ACT:4+4+3+4+4=19
- PFT:worsening
- Step up Relvar 200

- 20180919
- Symptom improved
- ACT:5+5+5+5+5=25
- Step down to Relvar 100

- 20180301
- On Relvar 100 for asthma control
- ACT:2+2+3+2+2=11
- Avoid exercise with GOLF

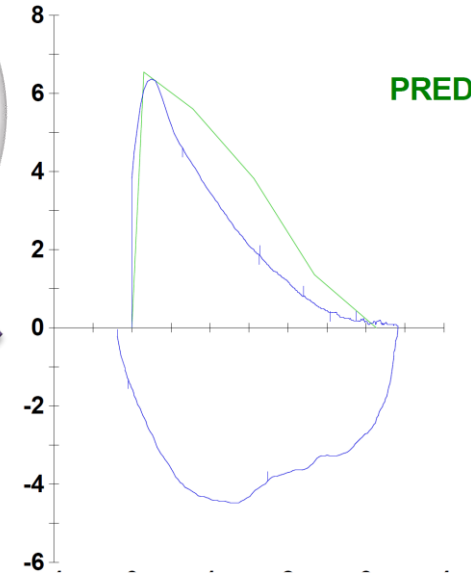
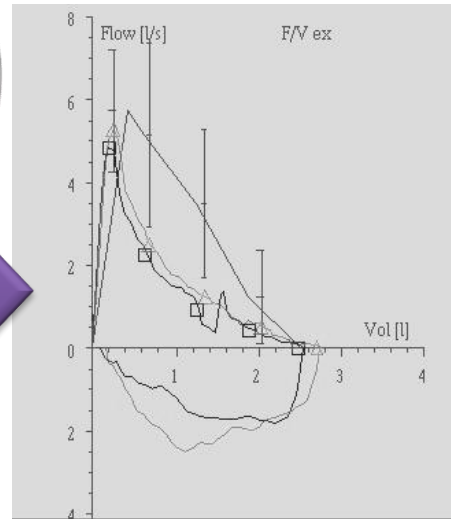
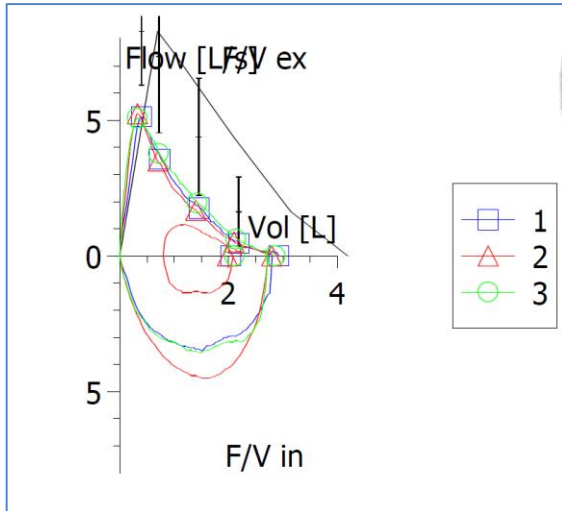
- 20180822
- On Relvar 200 for 3 months
- ACT:5+5+4+5+5=24
- Arrange PFT

- 20190122
- On Relvar 100 for 4 months
- ACT:5+5+5+5+5=25
- Arrange PFT

20180524 PFT

20180822

20190122



FEV1/FVC: **68.4%**

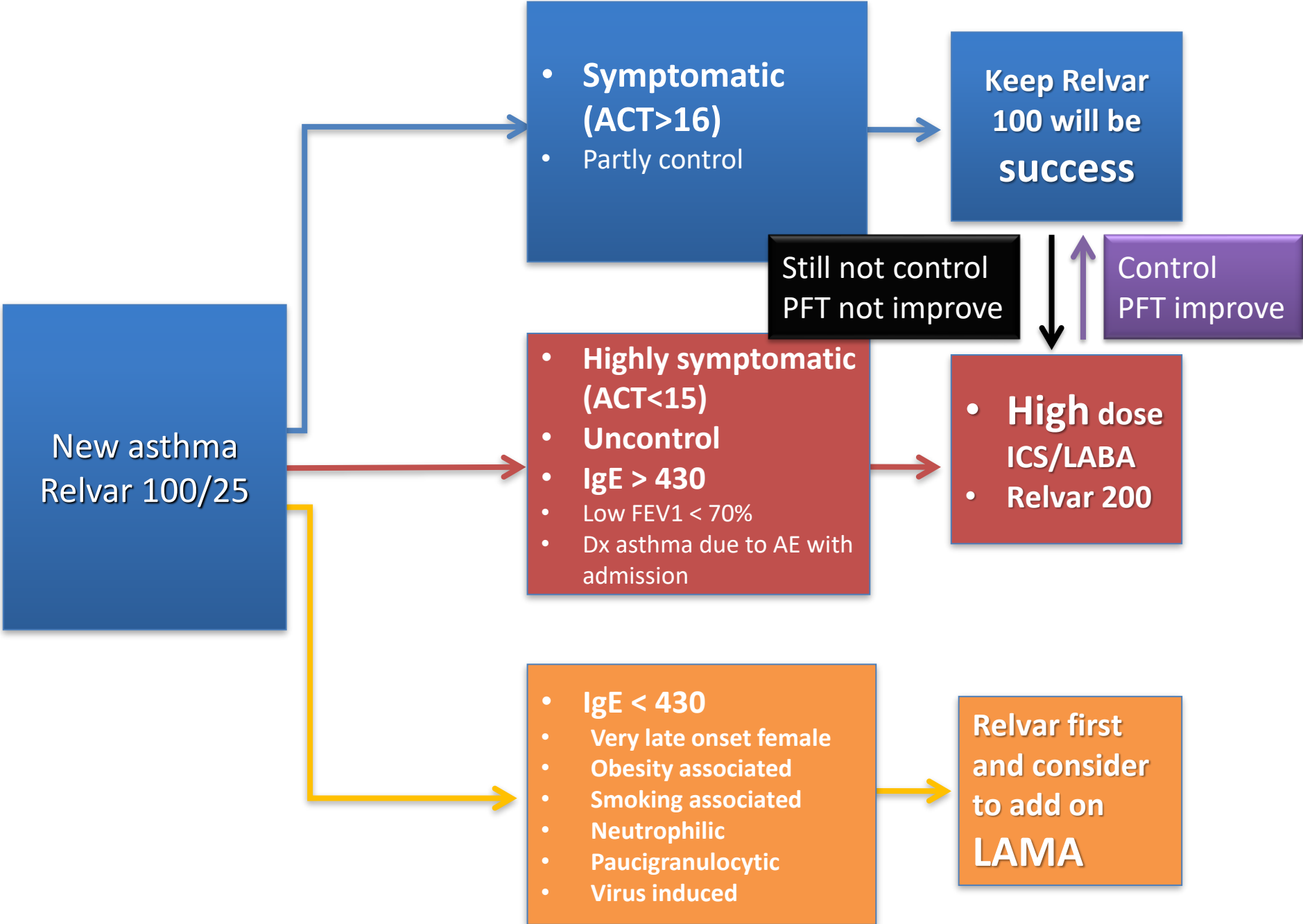
FEV1: **2.33L (69.1%)**

FEV1/FVC: **66%**

FEV1: **2.54L (75.3%)**

FEV1/FVC: **75.4%**

FEV1: **2.83L (83.9%)**



Stepwise treatment to achieve total asthma control

恢復區
RECOVERY AREA



中國附醫

陳家弘