Step-down approach in chronic stable asthma:
A comparison of reducing dose Inhaled Formoterol/
Budesonide with maintaining Inhaled Budesonide.

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Introduction

- Definition : Asthma is a chronic inflammatory disorder of the airways leading to airway hyper-responsiveness and associated variable airflow obstruction, that is often reversible either spontaneously or within treatment[1].

- Worldwide prevalence of asthma varies in adult population
    - United States: 7.1%[1]
    - Malaysia: 4.2%[2]

Introduction

- Treatment for asthma is tailored according to severity.

- In patients with moderate persistent asthma, the treatment of choice would be either a combination of inhaled corticosteroids (ICS) and a long acting $\beta 2$ agonist (LABA) or ICS alone.

- Greening et al[6] and Woolcock reported that inhaled LABA/ICS in combination therapy is more effective and well tolerated in asthma patients rather than increasing the maintenance dose of ICS.

- Various studies such as FACET, OPTIMA and GOAL have shown that inhaled LABA/ICS gave better asthma control than ICS alone[3,4,5]
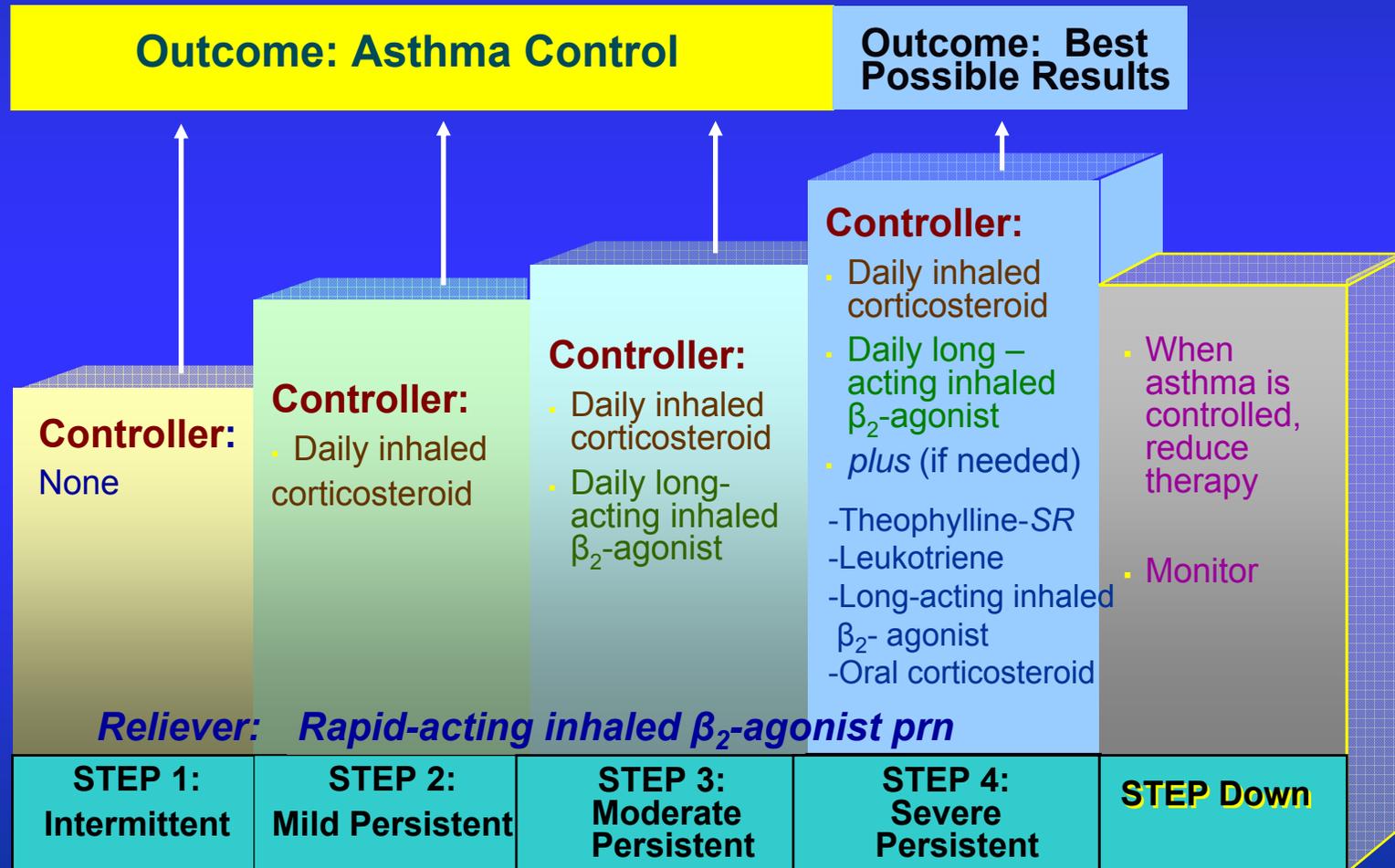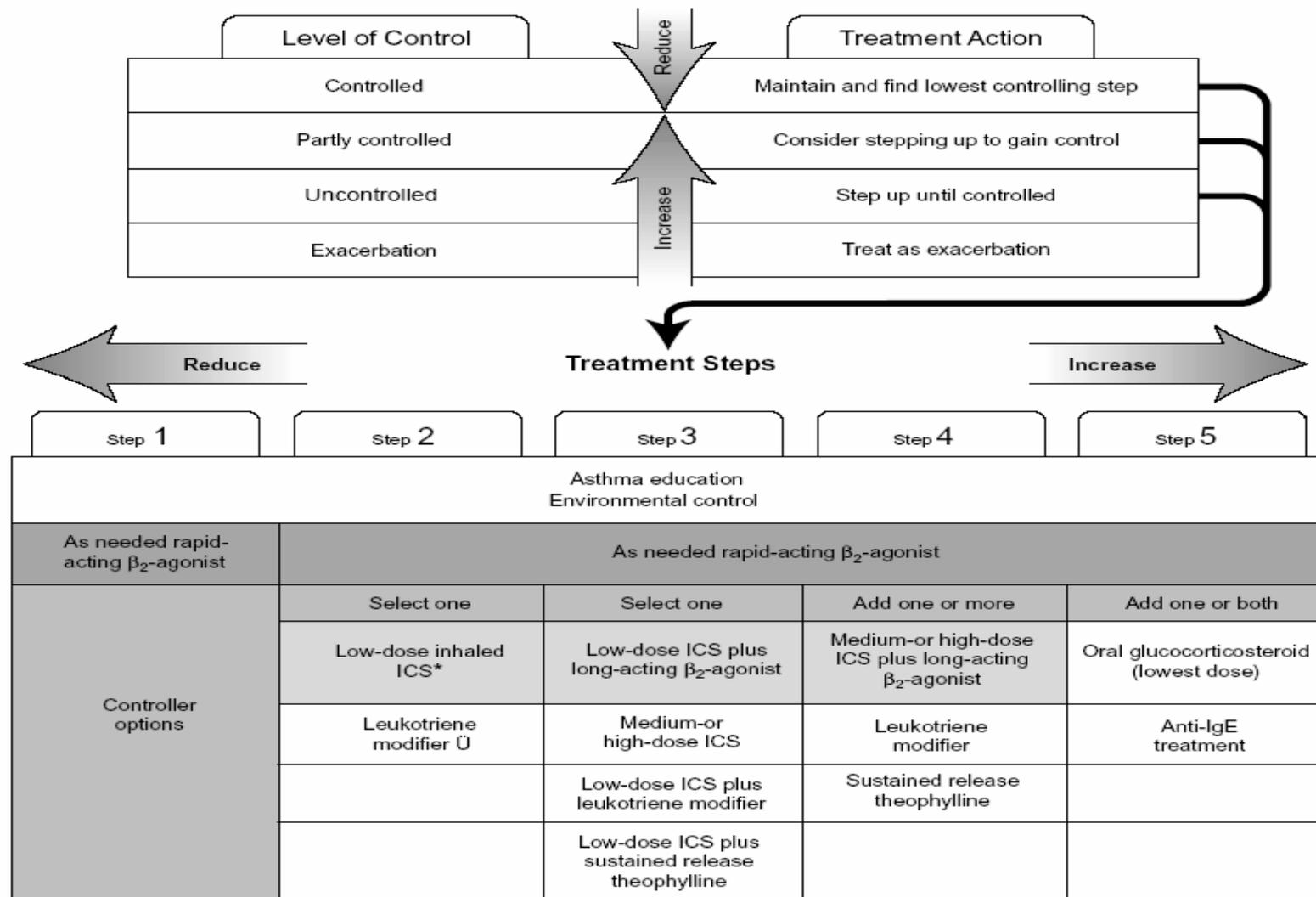
Stepwise Approach to Asthma Therapy

Outcome: Asthma Control

Outcome: Best Possible Results

Controller:
None

Controller:
- Daily inhaled corticosteroid

Controller:
- Daily inhaled corticosteroid
- Daily long-acting inhaled β_2-agonist

Controller:
- Daily inhaled corticosteroid
- Daily long – acting inhaled β_2-agonist
- *plus* (if needed)

-Theophylline-*SR*
-Leukotriene
-Long-acting inhaled β_2- agonist
-Oral corticosteroid

- When asthma is controlled, reduce therapy

- Monitor

Reliever: *Rapid-acting inhaled β_2-agonist prn*

STEP 1: Intermittent	STEP 2: Mild Persistent	STEP 3: Moderate Persistent	STEP 4: Severe Persistent	STEP Down

Figure 4.3-2.

Management Approach Based On Control

For Children Older Than 5 Years, Adolescents and Adults

Level of Control	Reduce / Increase	Treatment Action
Controlled		Maintain and find lowest controlling step
Partly controlled		Consider stepping up to gain control
Uncontrolled		Step up until controlled
Exacerbation		Treat as exacerbation

Treatment Steps

◄ Reduce   Increase ►

	Step 1	Step 2	Step 3	Step 4	Step 5
	Asthma education Environmental control				
As needed rapid-acting β$_2$-agonist	As needed rapid-acting β$_2$-agonist				
Controller options	Select one	Select one	Add one or more	Add one or both	
	Low-dose inhaled ICS*	Low-dose ICS plus long-acting β$_2$-agonist	Medium-or high-dose ICS plus long-acting β$_2$-agonist	Oral glucocorticosteroid (lowest dose)	
	Leukotriene modifier Ü	Medium-or high-dose ICS	Leukotriene modifier	Anti-IgE treatment	
		Low-dose ICS plus leukotriene modifier	Sustained release theophylline		
		Low-dose ICS plus sustained release theophylline			

* ICS=inhaled glucocorticosteroids
Ü=Receptor antagonist or synthesis inhibitors

Alternative reliever treatments include inhaled anticholinergics, short-acting oral β$_2$-agonists, some long-acting β$_2$-agonists, and short-acting theophylline. Regular dosing with short and long-acting β$_2$-agonist is not advised unless accompanied by regular use of an inhaled glucocorticosteroid.

Addition of LABAs to inhaled corticosteroids was associated with a lower exacerbation rate than doubling the dose of inhaled corticosteroids

Study	Participants, No.	Age, y, Mean (SD)*	FEV, % Predicted, Mean (SD)*	Favors Steroids and LABA / Favors Higher Dose Steroids
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: $\chi^2 = 6.88$, $P = .65$)

Relative Risk (95% Confidence Interval)
0.0   0.5   1.0   1.5   2.0   2.5

Sin et al JAMA 2004;292: 367-376

Introduction

- Hawkins et al reported that a reduction in the dose of ICS could be achieved without compromising asthma control[4].

- For those treated with combination of LABA/ICS, step-down approach could be attempted by either reducing the dose of LABA/ICS or stop the LABA and maintain the ICS at the same dosage.

Research hypothesis

- The efficacy of treatment response in patients with dose reduction using inhaled formoterol/budesonide combination is superior to treatment response in patients using maintenance inhaled budesonide only.

Objectives

- **Primary objective:**

  To compare the efficacy of reduced dose of formoterol/budesonide Turbuhaler with the same dose of budesonide Turbuhaler as a step-down approach in chronic stable asthma. The primary efficacy variable was morning forced expiratory volume in 1 second (FEV_1).

- **Secondary objectives:**

  To compare the peak expiratory flow rate (PEFR), asthma control test (ACT) score, asthma related events and asthma exacerbation rates between the two groups.

Study Design

- Open labeled, randomized parallel group design with two step-down treatment groups.

- The study was carried out between March 2006 until September 2006.

Sample size and power calculation

- **Sample size calculation[5,6] :**

$$n = \frac{2(A + B)^2 \sigma^2}{(\delta)^2}$$

n = **The sample size required in each group**
A = **Desired significance level of 5% = 1.96**
σ = **Standard deviation of difference**
B = **Desired power of study (80%) = 0.84**
δ = **size of difference of clinical importance**

- **Assuming a standard deviation of 0.25 liters and the requirement for 80% power, it was calculated that data for 50 evaluable patients would be required to demonstrate a difference of 0.2 liters with 95% confidence.**

Table of values for *A* and *B*	
Significance level	**A**
5%	1.96
1%	2.58
Power	**B**
80%	0.84
90%	1.28
95%	1.64

Inclusion criteria

- Age $\geq$ 18 years

- Asthma for at least one year.

- On treatment with Formaterol 4.5μg/Budesonide 160μg Turbuhaler 2 inhalations b.i.d. for $\geq$ 6 months

- Good asthma control based on asthma control test (ACT) score of $\geq$ 20 for at least 1 month prior to randomization.

- Gave written informed consent.

Exclusion criteria

- Asthma control test score $\leq$ 19.

- Inability to carry out pulmonary function test.

- Diagnosis of COPD according to GOLD guidelines

- Current smoker or ex-smoker $\geq$ 5 pack-years.

- Serious medical illnesses such as congestive heart failure, recent myocardial infarction, severe uncontrolled hypertension, cardiac arrhythmias, or uncontrolled diabetes mellitus.

- Patients treated with a xanthine derivative (e.g. theophylline) or leukotriene antagonists in the 4 weeks prior to study start.

- Pregnant or lactating females,

- History of alcohol, drug or substance misuse.

Methodology

Recruitment based on ACT $\geq$ 20
Initial dose of formoterol/budesonide
2 puffs b.i.d.
(n=50)

Group A
Patient with formoterol/budesonide
Turbuhaler at 50% reduction of dose
@ 1 puff b.i.d.
(n = 25)

Group B
Patient with budesonide Turbuhaler
@ 400 µgm b.i.d.
(n = 25)

Clinic visits at week 0,6 and 12

Clinic visits at week 0,6 and 12

- Approved by HUKM research and ethics committee.

1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much work done at work, school or at home ?

1	2	3	4	5
All the time	Most of the time	Some of the time	A little of the time	None of the time

2. During the past 4 weeks, how often have you had shortness of breath ?

1	2	3	4	5
All the time	Most of the time	Some of the time	A little of the time	None of the time

3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning ?

1	2	3	4	5
All the time	Most of the time	Some of the time	A little of the time	None of the time

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as salbutamol) ?

1	2	3	4	5
All the time	Most of the time	Some of the time	A little of the time	None of the time

5. How would you rate your asthma control over the past 4 weeks ?

1	2	3	4	5
All the time	Most of the time	Some of the time	A little of the time	None of the time

Asthma Control Test[7]

Total control = 25

Outcome measures

- **The primary outcome:**

  Morning FEV_1 assessed at clinic visits using spirometry (vitalograph).

- **The secondary outcomes:**

  Morning PEFR at clinic visits, daily FEV_1/PEFR record from pikometer, ACT score, asthma related events and asthma exacerbations.

  – Clinic PEFR was recorded using Wright[®] peak flow meter.

 – The patient recorded daily FEV_1 and PEFR using Pikometer (electronic FEV_1/PEFR meter).

Pikometer

Statistical analysis

- The data were analyzed using SPSS version 12.

- The student t-test was used for comparison between the two groups. All normally distributed numerical data were expressed as mean $\pm$ standard deviation.

- Chi-square test and Fischer`s Exact test were used for qualitative data.

- A p value < 0.05 was considered significant.

Results & Discussion

Baseline characteristic and demographic data between the two groups

|	Formoterol/Budesonide Group (n=25)	Budesonide Group (n=25)	p value
Age in years (mean $\pm$ SD)	48.76 $\pm$ 11.55	47.92 $\pm$ 9.77	0.783
Gender (Male : Female)	3 : 22	9 : 16	0.095
Race (Malay:Indian:Chinese)	17 : 6 : 2	19 : 4 : 2	0.774
FEV_1 in liters (mean$\pm$SD)	1.52 $\pm$ 0.52	1.75 $\pm$ 0.64	0.171
PEFR in liters/minute (mean $\pm$ SD)	288.40 $\pm$ 68.40	327.80 $\pm$72.68	0.055
Mean duration of asthma (years) (mean $\pm$ SD)	25.08 $\pm$ 9.72	20.3 $\pm$ 10.68	0.100
Mean duration of formoterol/budesonide (months) (mean $\pm$ SD)	19.92 $\pm$ 7.42	18.08 $\pm$ 4.88	0.307
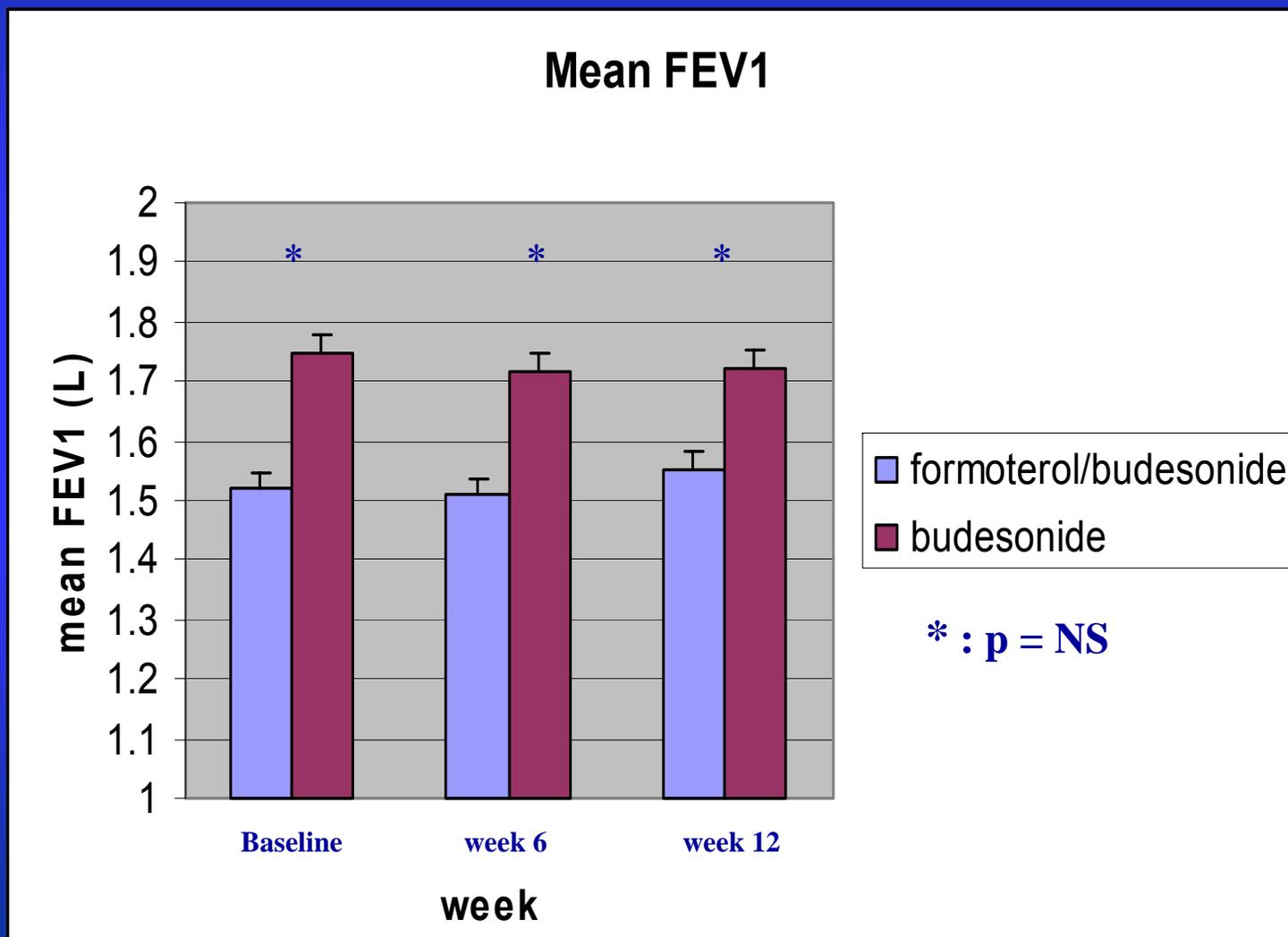
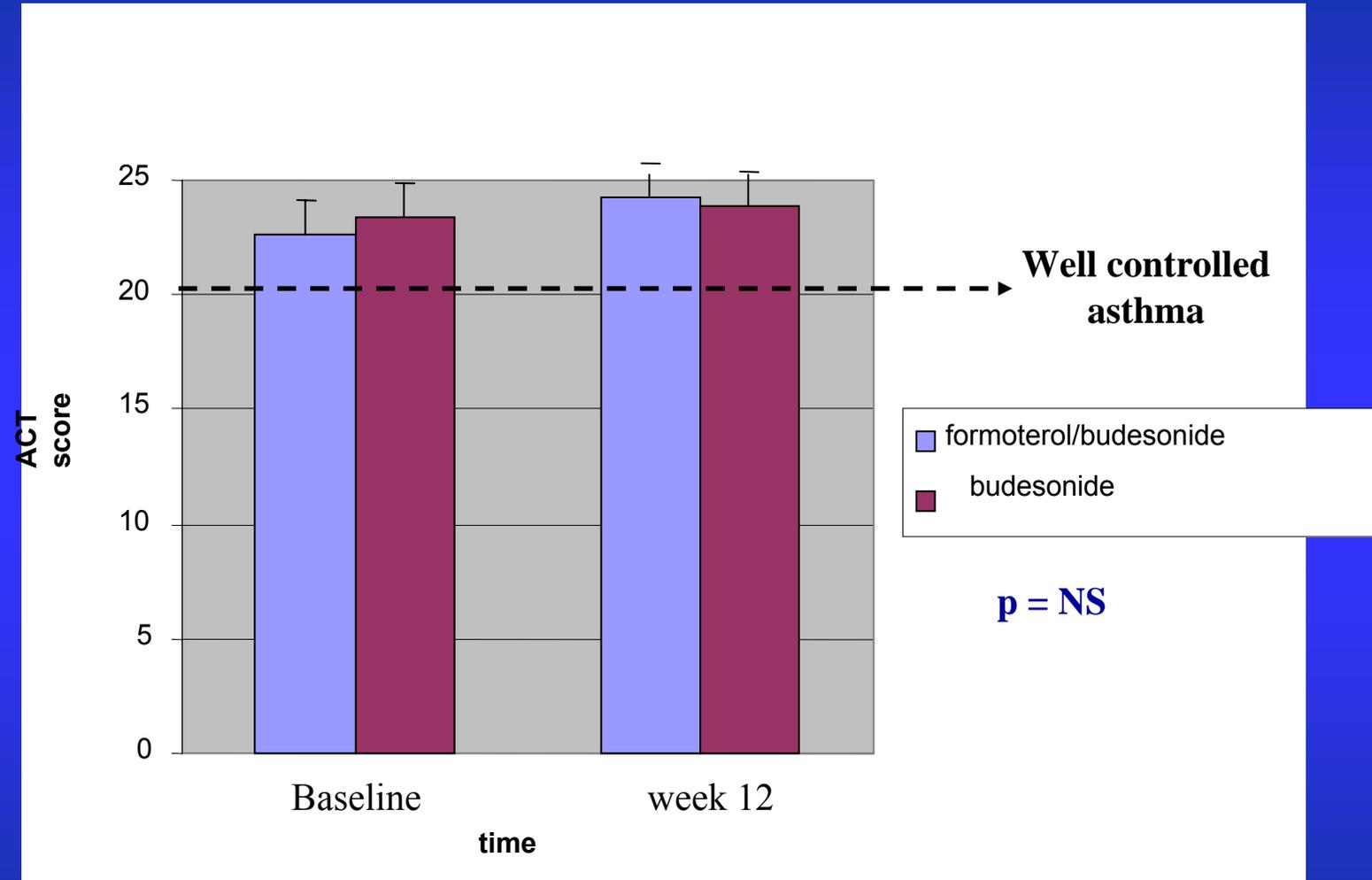# Daily Morning FEV$_1$ (pikometer)

changes in mean FEV1

mean FEV1 (L)

week

formoterol/budesonide
budesonide

p = NS
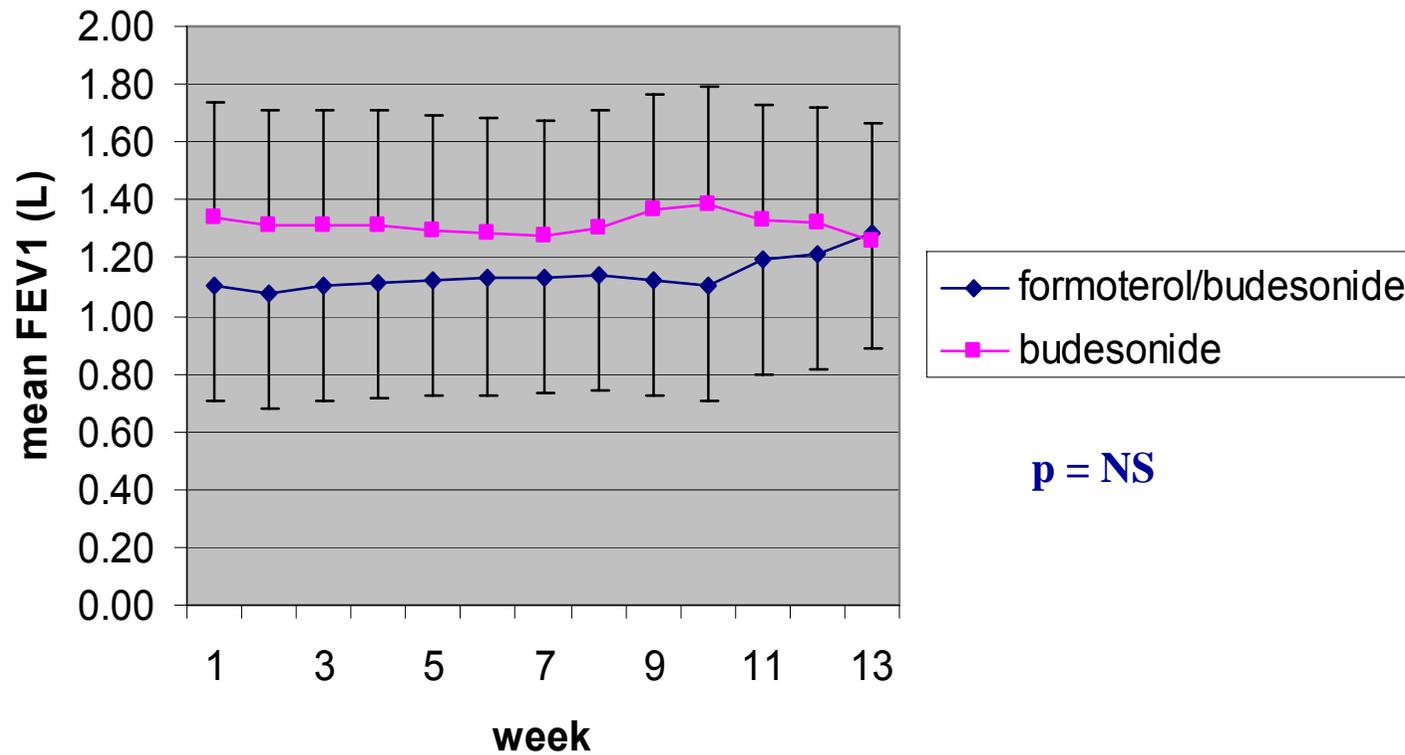
Clinic PEFR
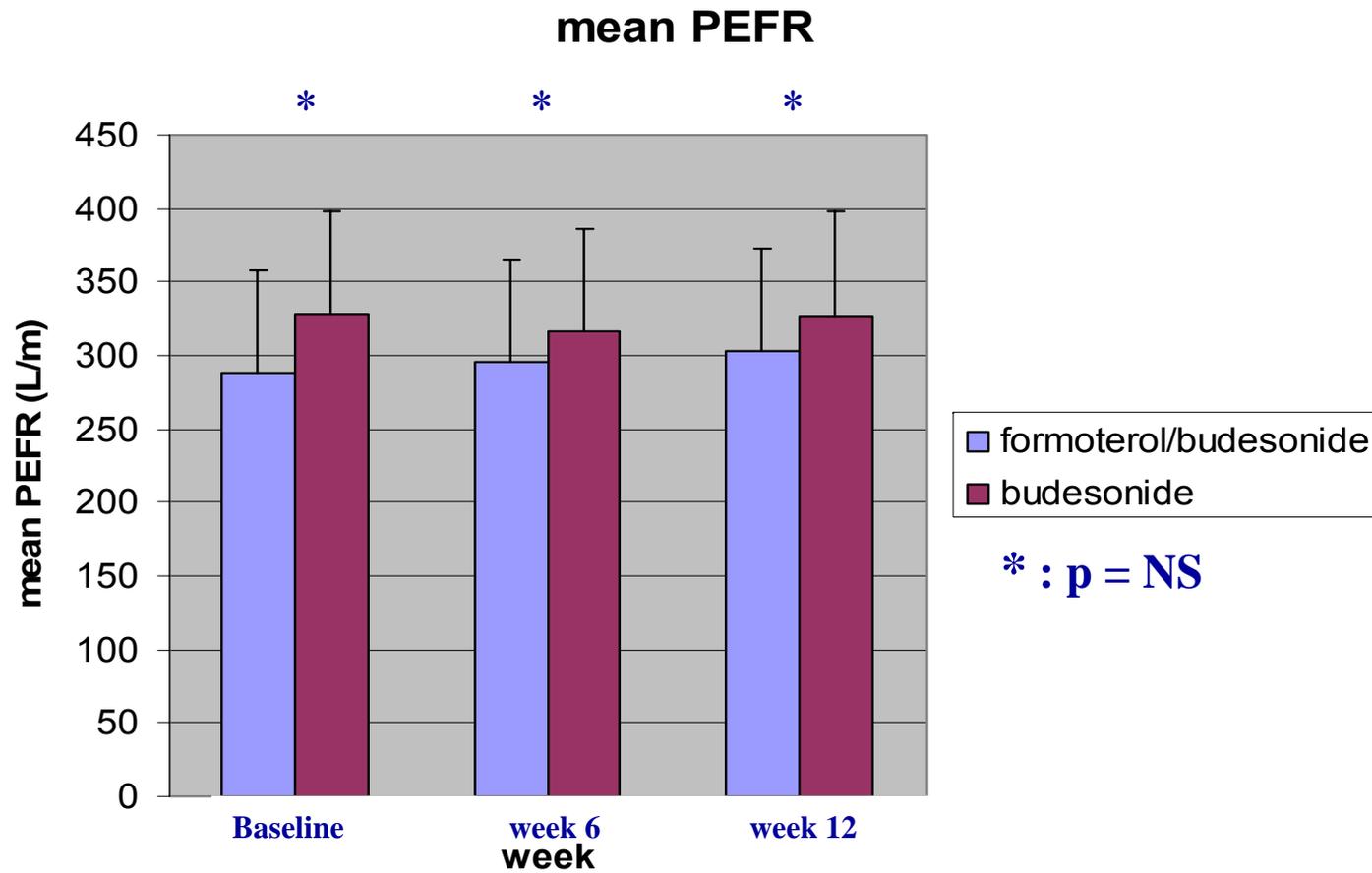
Daily morning PEFR (pikometer)

changes in mean PEFR
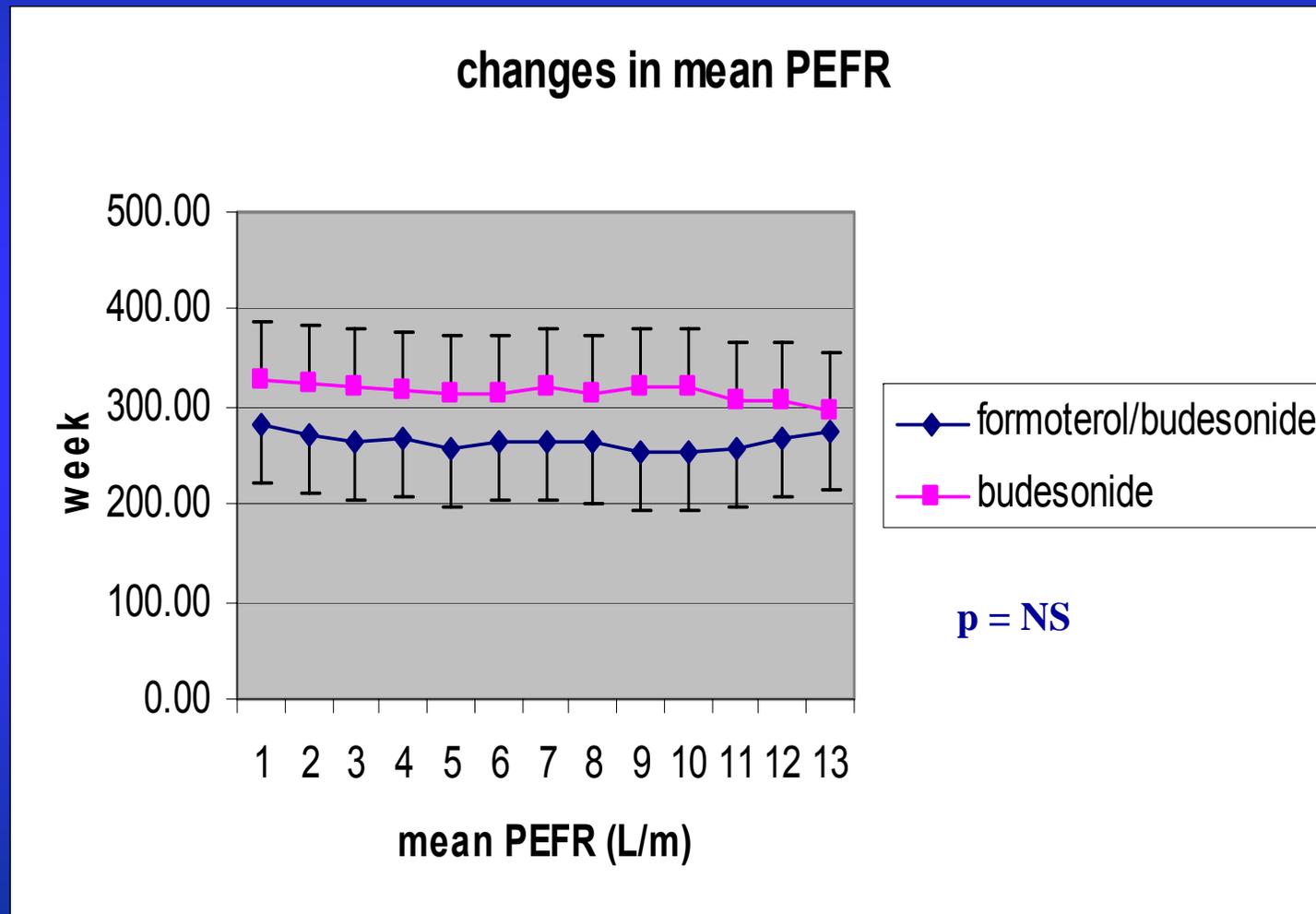
Asthma related events and asthma exacerbation

- One patient from the budesonide group had an acute exacerbation during the study period requiring a course of oral steroid → recovered fully.

- No events or exacerbation were reported from the combination group.

Study limitations

- Difficult to recruit patient due to lack of patient`s confidence to step down therapy.

- Pikometer : FEV_1 reading < clinic FEV_1
  - Advantage of Pikometer : prevent manipulation of data compared to diary card.

- Duration of the study is too short to detect asthma exacerbation and whether the lung functions continue to be stable after 3 months.

Conclusions

Conclusions

- Formoterol 4.5µg/budesonide 160µg Turbuhaler was as efficacious as budesonide 400 µg/day Turbuhaler as step-down approaches for asthma patient

- There were no significant difference in the FEV_1, PEFR, asthma control test (ACT) score, asthma related events and asthma exacerbation rates between the two groups.

References

1. Global Initiative For asthma (GINA).WR Draft 2003; updated 28/10/2004.
2. National Health and Morbidity Survey II 1996, Ministry of Health, Malaysia.
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4. Hawkins G et al. *BMJ 2003*;326:1110-1115
5. Lwanga SK, Lemeshaw S. *WHO 1991*, Geneva.
6. Jones SR et al. *Emerg Med J* 2003;20:453-458.
7. Schatz M et al. *Am J Respir Crit care Med* 2003;167:A38.

Thank you