

Review of asthma trials and proportion of patients eligible in clinical practice^{1,2}

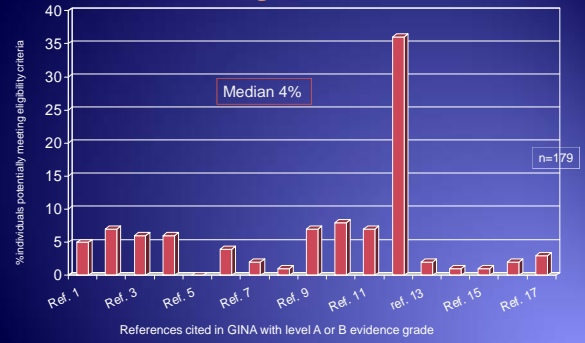
Table 4 Selectivity of eligibility criteria

Criterion	Participants with current asthma excluded (%)
Bronchodilator reversibility $\geq 1.5\%$	76
Bronchodilator reversibility $\geq 1.2\%$	71
Peak flow variability $\geq 20\%$	66
FEV ₁ $\geq 50\%$ and $< 80\%$ of predicted	61
Inhaled corticosteroid use	48
< 10 pack-years of exposure to cigarette	31
Active symptoms or use of rescue drugs	20
FEV ₁ $\geq 50\%$ of predicted	12

Current reversibility precludes 75% + of patients
In Australia 7-18% meet criteria depending on level²

1. Travers J, Marsh S, Williams M, Weatherall M, Caldwell B, Shirtcliffe P, Aldington S, Beasley R. External validity of randomised controlled trials in asthma: to whom do the results of the trials apply? *Thorax*. 2007;62:219-23.
2. Appleton SL, Adams RJ, Wilson DH, et al. Spirometric criteria for asthma: adding further evidence to the debate. *J Allergy Clin Immunol* 2005;116:976-82.

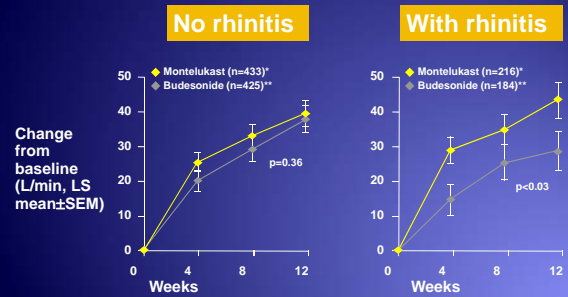
External validity of RCTs in asthma guidelines...



Travers *et al.* *Thorax* 2007

Does it matter?

Differential efficacy of Add-on Montelukast vs ICS increase in Asthma Patients with Concomitant Allergic Rhinitis



*Montelukast 10 mg once daily + budesonide 400 µg twice daily; **Budesonide 800 µg twice daily
Price DB *et al.* *Allergy* 2006

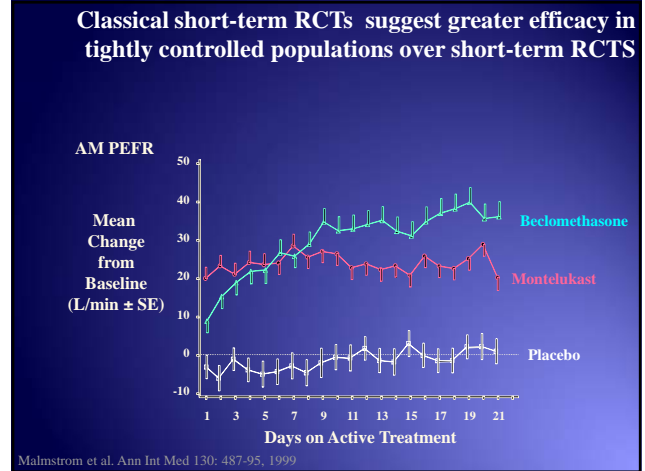
101 British Guideline on the Management of Asthma
A national clinical guideline

INHALED STEROIDS

Inhaled steroids are the most effective preventer drug for adults and older children for achieving overall treatment goals.²⁷⁹⁻²⁸² There is an increasing body of evidence demonstrating that, at recommended doses, they are also safe and effective in infants and younger children with asthma.²⁸³⁻²⁸⁶

>12 years	5-12 years	<5 years
1**	1**	1**

May 2008



Why ELEVATE

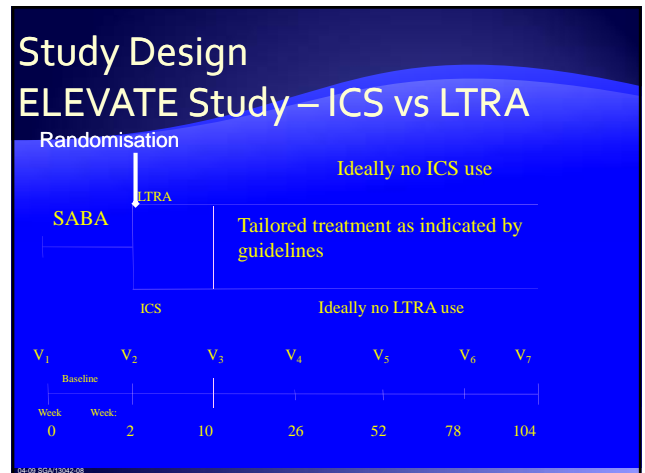
- HTA wanted to assess effectiveness and cost-effectiveness

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Leukotriene Antagonists as First-Line or Add-on Asthma-Controller Therapy

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Key points re pragmatic trials

- Designed to answer important questions facing patients, clinicians, and policymakers.
- Compare medical interventions directly relevant to clinical care or health care delivery and strive to assess those interventions' effectiveness in real-world practice.
- Use broad eligibility criteria and recruit patients from variety of settings to include patients whose care will be influenced by results.
- Medical management consistent with usual clinical care – often omitting procedures such as blinding that alter “ecology” of care.
- Ideally, measure all outcomes important to patients and decision makers
- Treatment duration and follow-up sufficient to adequately assess treatments' benefits and risks.

Strengths and weaknesses

- Changeover of treatment may lead to greater likelihood of equal results
- Open-label essential may bias patient and physician response and behaviour
 - Need objective as well as subjective outcome
 - Exacerbations and lung function
 - Physicians more likely to change non-guideline treatment
- Follow-up rates need to be high

Inclusion criteria

- Age ≥ 12 years
- Physician diagnosed asthma
- PEF $> 50\%$ predicted while withholding β_2 agonist for ≥ 4 hours
- Asthma Control Questionnaire score of ≥ 1 point and Mini Asthma Quality of Life Questionnaire of < 6 points

Demographics and drop out rates

Comparison to another key classical RCT

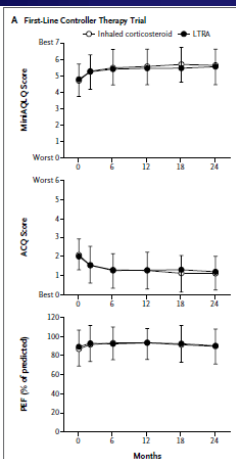
	ELEVATE Step 2; N=306	GOAL Strata 2; N=1163
Sex (% Female)	51%	59%
Age *	45.8 (16.4)	40.4 (16.5)
Quality of Life (Juniper AQLQ 1, worst, to 7)	4.74 (1.04)	4.6 (1.1)
Lung Function *	86 %PPEF	78 %PPEF
Percent reversibility *	8.9% (9.86)	(Median = 22% ≥13% for eligibility)
Smokers – current	21.9%	6% (<10 pack-yr for eligibility)
Drop out rate	4.0%	15.4%

* = Mean (SD), NR = not reported, NA = not applicable, %PPEF= Percent predicted PEF, %PPEF1= Percent predicted FEV1

1- Bateman et al. AJRCCM. 170. p.836, (2004); 2- Bjerner et al. BMJ. 327. p.891, (2003)

The problems

- Recruiting real-life doctors and real-life patients
- Equipose rarely exists in medical decisions
 - Doctors increasingly follow guidelines – making pragmatic trials difficult
 - Switch to standard care inevitable in a proportion of patients



Outcome Measure	LTRA		Inhaled Glucocorticoid		Mean Difference [95% CI]	Adjusted Mean Difference [95% CI]
	no. of patients tested	mean score	no. of patients tested	mean score		
First-line controller therapy trial						
ITT MiniAQOLQ						
At baseline	148	4.75±0.92	158	4.72±0.95		
At 2 mo	122	5.25±1.03	132	5.28±1.10	0.00 (-0.25 to 0.26)	-0.02 (-0.24 to 0.20)
At 2 yr ¹	145	5.52±1.07	155	5.63±1.16	-0.10 (-0.35 to 0.17)	-0.11 (-0.35 to 0.13)
PP MiniAQOLQ						
At 2 mo	115	5.26±1.02	127	5.35±1.04	-0.09 (-0.35 to 0.18)	-0.08 (-0.31 to 0.15)
At 2 yr	98	5.61±1.03	120	5.65±1.16	-0.04 (-0.34 to 0.25)	-0.12 (-0.38 to 0.14)
ITT ACO						
At baseline	148	1.99±0.70	158	2.06±0.84		
At 2 mo	123	1.54±0.93	132	1.53±1.00	-0.02 (-0.24 to 0.21)	0.01 (-0.20 to 0.22)
At 2 yr ¹	145	1.23±0.95	155	1.15±0.92	0.10 (-0.11 to 0.32)	0.13 (-0.07 to 0.33)

Outcome Measure	Treatment Group		Rate Ratio (95% CI) [†]	P Value
	LTRA (N=148)	Inhaled Glucocorticoid (N=158)		
First-line controller therapy trial				
Asthma exacerbations				
Any — no. of exacerbations	0.44±0.94	0.35±0.95	1.27 (0.83–1.92)	0.23
1 — no. of patients/total no. (%)	19/148 (13)	13/158 (8)		
>1 — no. of patients/total no. (%)	17/148 (11)	14/158 (9)		
Adherence				
No. of patients	108	101		
Rate — %				0.11
Median	65	41		
Interquartile range	15–92	21–62		

Table 4. Changes in Treatment According to the Assigned Treatment.^a

Treatment Change	No. of patients (%)	Inhaled glucocorticoid, first-line controller therapy trial
LTRA, first-line controller therapy trial		
Total in group	145	Total in group 155
Changes at 2 mo		
Crossed over to inhaled glucocorticoid	6	Added LABA 3
Crossed over to inhaled glucocorticoid plus LABA	1	Crossed over to LTRA 2
Had multiple changes	1	Total 5 (3.2)
Total	8 (5.5)	Changes at 2 yr
Changes at 2 yr		
Added inhaled glucocorticoid	4	Added LABA 28
Added inhaled glucocorticoid and LABA	2	Crossed over to LTRA 4
Crossed over to inhaled glucocorticoid	27	Total 32 (20.6)
Crossed over to inhaled glucocorticoid and LABA	8	
Crossed over to inhaled glucocorticoid, then added LABA	3	
Had multiple changes	1	
Total	45 (31.0)	

Was Sir Michael Rawlings Right?

Journal Club

Evidence-Based Medicine

■ THERAPEUTICS

Low-dose inhaled corticosteroids (ICS) reduce asthma exacerbations in patients with mild to moderate asthma. [23](#)

Low-dose ICS reduce asthma exacerbations in patients with mild to moderate asthma. [24](#)

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