Role of LAMA in asthma

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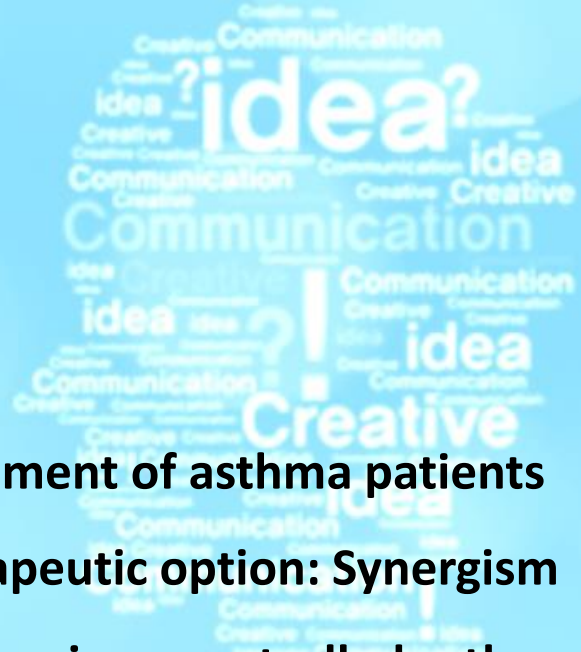

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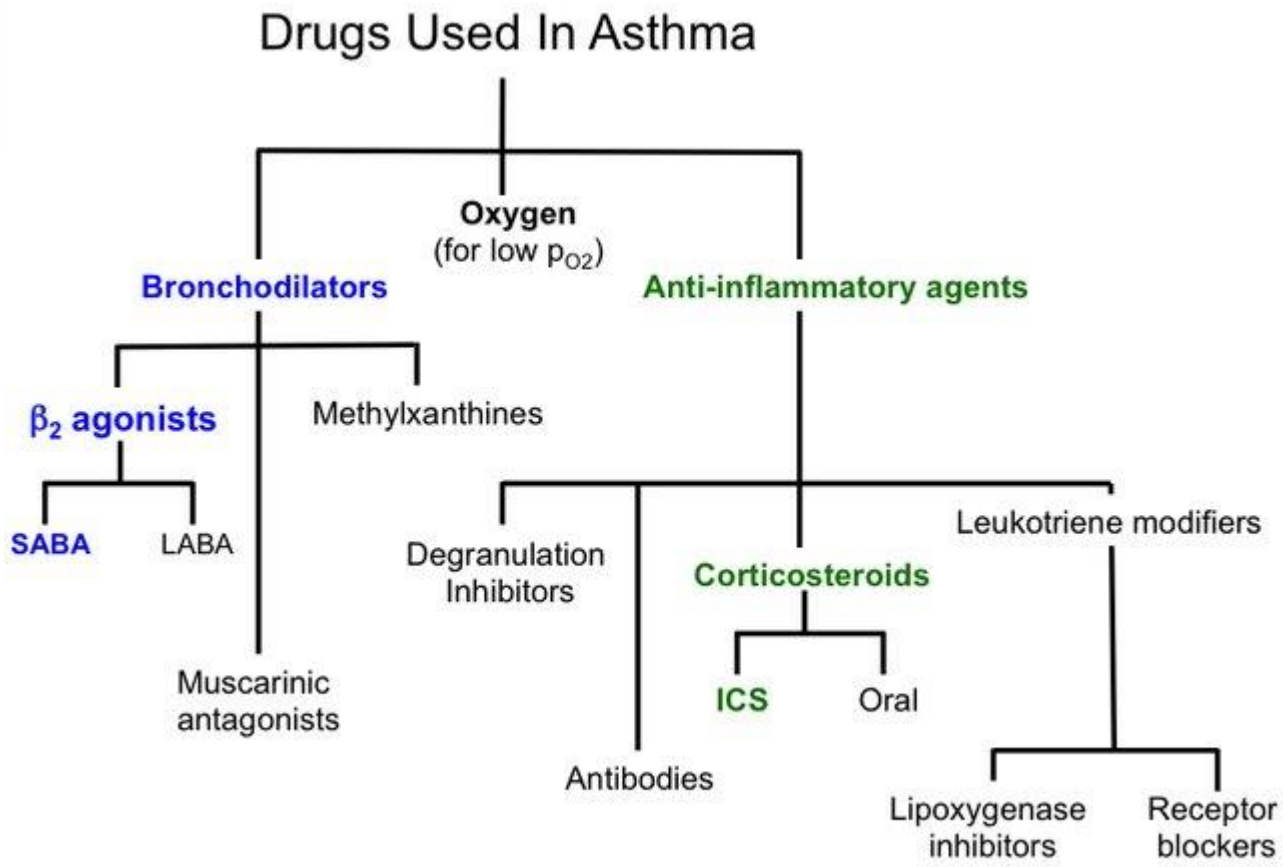
1. LAMA in current management of asthma patients

About asthma

- Asthma is the most common chronic non-communicable disease, affecting over 260 million people globally in 2019
- Asthma is characterized by **variable respiratory symptoms** such as wheeze, shortness of breath, chest tightness and cough, and **variable expiratory airflow limitation**. It is usually associated with **airway inflammation**
- People with asthma often have periods of worsening symptoms and worsening airway obstruction, called **exacerbations** (also called attacks or flare-ups), that can be fatal
- Most of the morbidity and mortality associated with asthma is preventable, particularly with use of inhaled corticosteroids

Global strategy for asthma management and prevention updated 2021

Pharmacology in asthma



World Journal of Advanced Research and Reviews, 2020, 08(03), 059-070

Bronchodilators in asthma

β2-adrenergic agonists

Theophylline

Anticholinergics (Antimuscarinics)

Airway pharmacology in asthma

- In the early 1800s, there were many “asthmas,”

since this was the term for any episodic shortness of breath.

Figure 1. Asthma Cigarettes.

Asthma cigarettes made from the leaves of *Datura stramonium* (thorn apple) were widely sold in the 1800s and into the early 1900s. These cigarettes provided a means of delivering an inhaled treatment; we now know that the active component of this smoke was antimuscarinic alkaloid. Antimuscarinic treatment of asthma has recently been studied with the use of chemically synthesized moieties, such as tiotropium bromide and ipratropium bromide. Images courtesy of Mark Sanders, www.inhalatorium.com.

- Once a diagnosis of asthma (as we know it now) was established,
  - the number of effective treatments was quite limited
  - Inhalation of smoke from burning **Datura stramonium**
    - anticholinergic properties and the forerunner of antimuscarinic agents, such as ipratropium and tiotropium.
  - other treatments
    - inhalation of the fumes of hydrocyanic acid or inflation of the lungs with a bellows
      - harmful , no longer used.

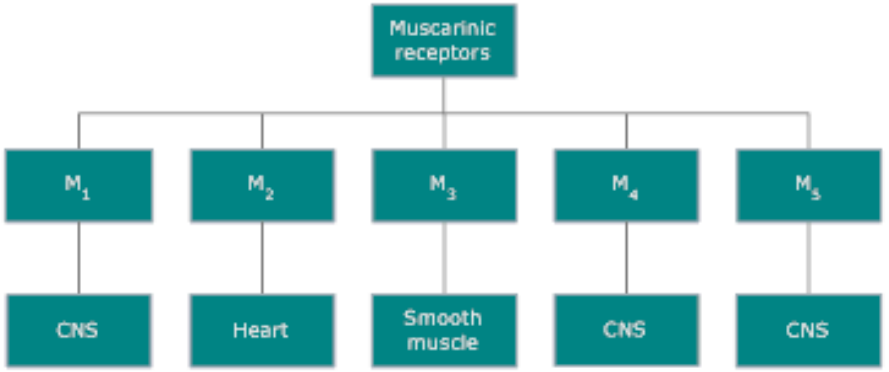
Asthma Cigarettes

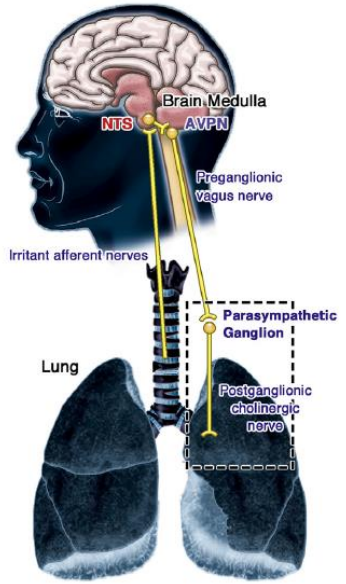
Antimuscarinic treatment

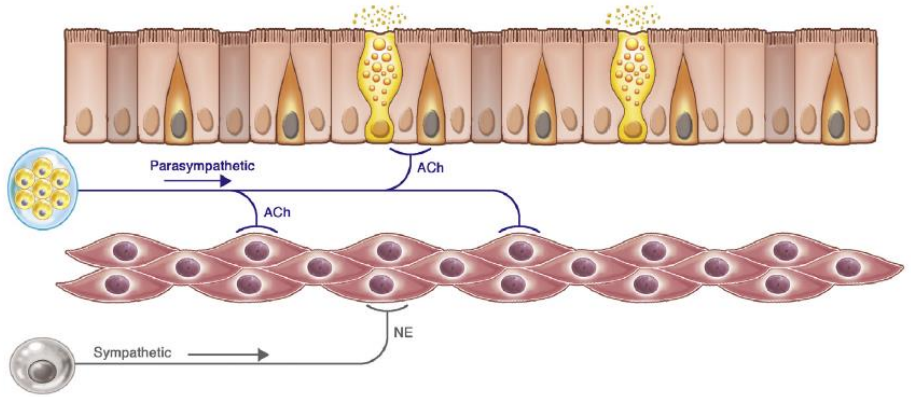
Mutius E, et al. NEJM 2012;366:727-34.

Mechanism of action of muscarinic antagonists

- **Parasympathetic nervous system**
  - **Cardiac conduction system**
  - **Exocrine glands**
  - **Smooth muscles**
- Sympathetic nervous system
  - Sweat glands
- Central nervous system





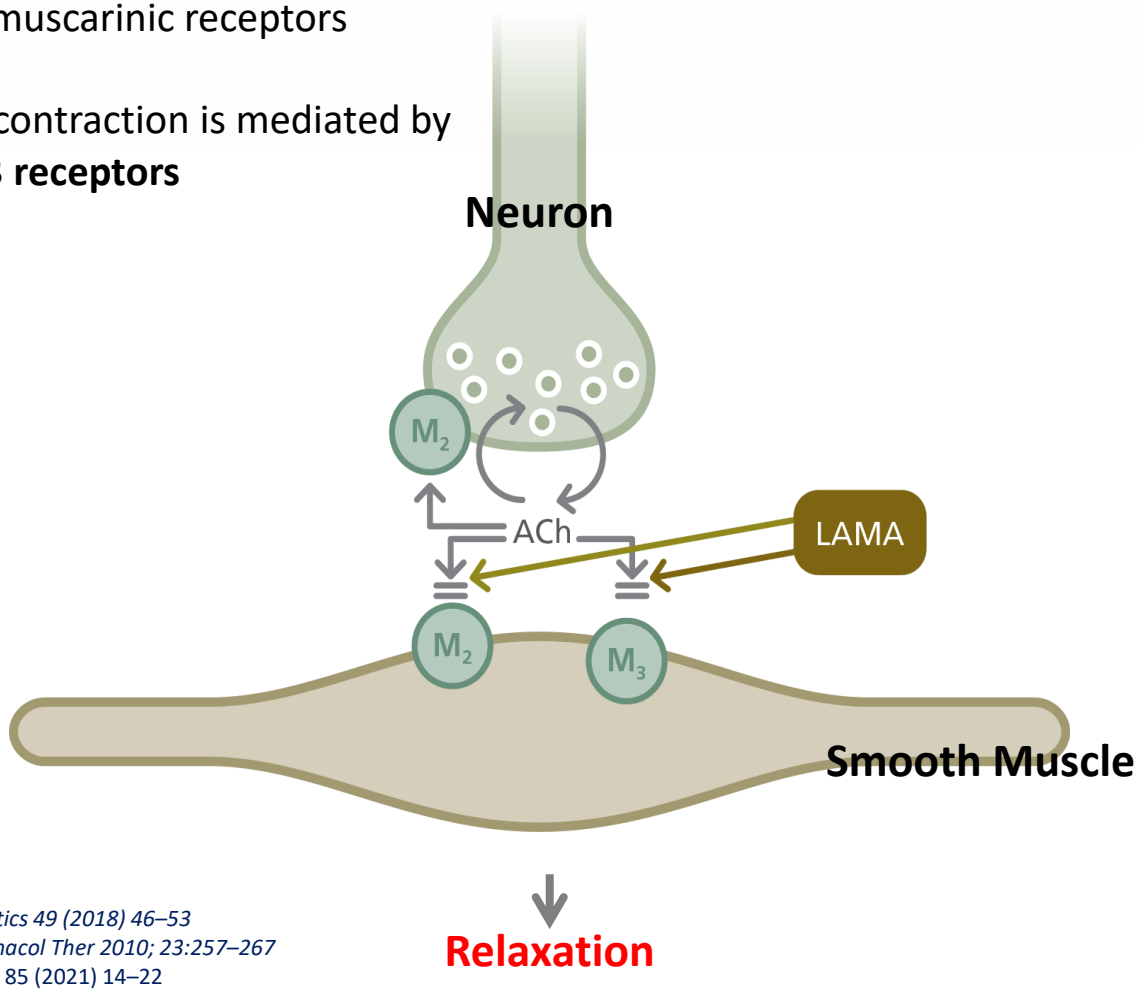


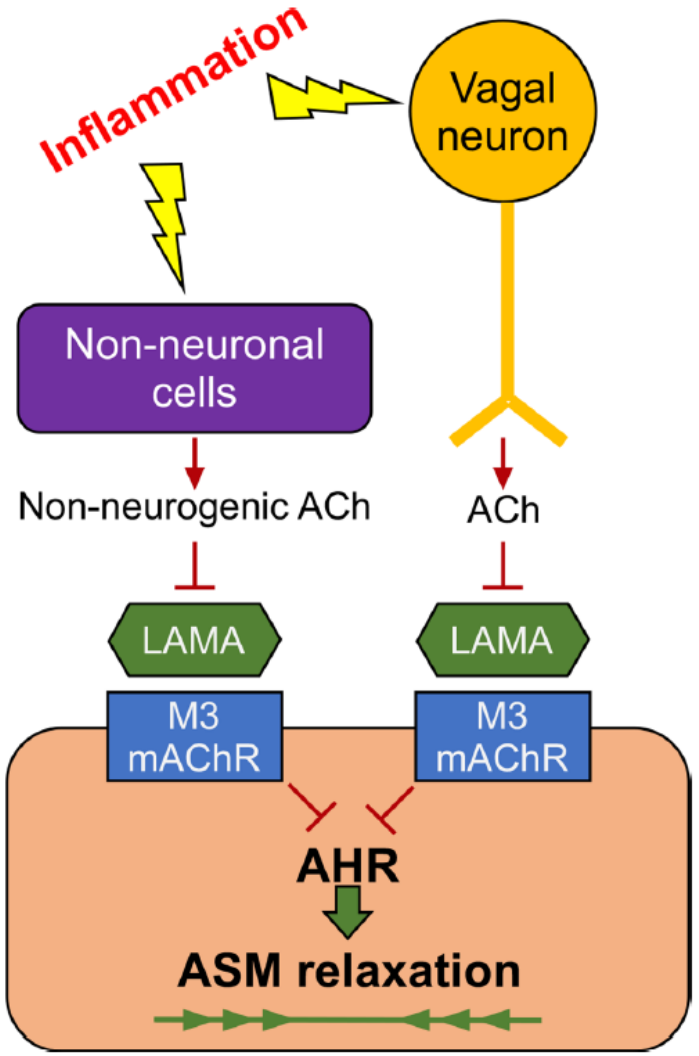
Nature Reviews Drug Discovery volume 6, pages 721–733 (2007)
Image adopted from pharmacology.com
J Allergy Clin Immunol 2020;146:1288-91

Mechanism of action of muscarinic antagonists

Human airway smooth muscle expresses both M2 and M3 muscarinic receptors

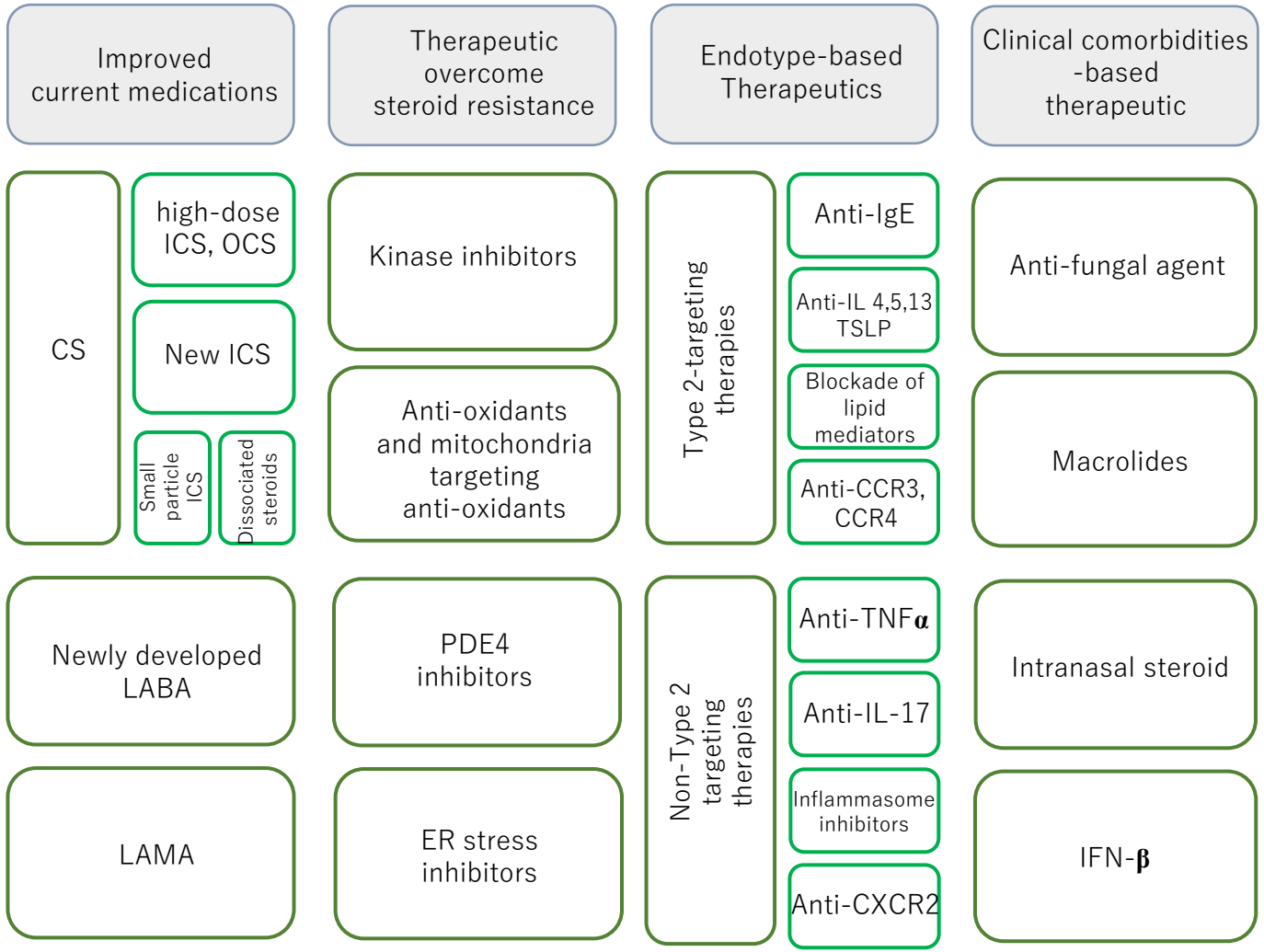
The ACh-induced contraction is mediated by **stimulation of M3 receptors**





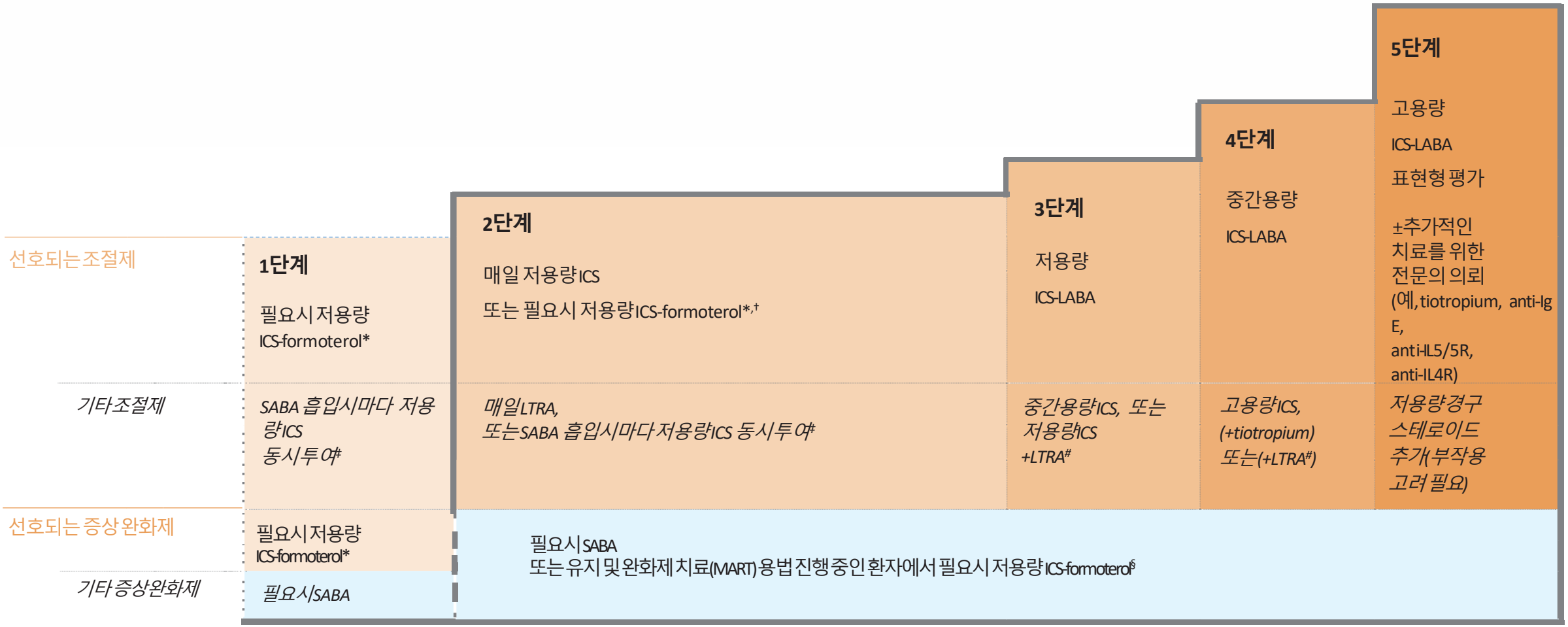
Pulmonary Pharmacology & Therapeutics 49 (2018) 46–53
Cazzola M & Molimard M. Pulm Pharmacol Ther 2010; 23:257–267
European Journal of Internal Medicine 85 (2021) 14–22

Pharmacologic therapeutic approaches for severe asthma



Kim SR. Pharmacologic therapies for severe asthma In: Severe asthma: Toward Personalized patient Management (doi.org/10.1007/978-981-10-1998-2)

2020 KATRD asthma guideline



Off-label; budesonide-formoterol 관련자료만존재

*Off-label; 개별적이거나 혼합치료로써의 ICS와 SABA 흡입제
§저용량 ICS-form은 bud-form or BDP-form 유지 및 완화제 치료 (SMART 혹은 MART)의경우 가능
#FEV_1>70%이며 알레르기성 비염 동반하는 감작된 환자에서 집먼지 진드기 설하면역치료 고려

2020 The Korean Academy of Tuberculosis and Respiratory Disease(KATRD) Asthma guideline 4nd edition

Japanese Society of Allergology guideline 2020

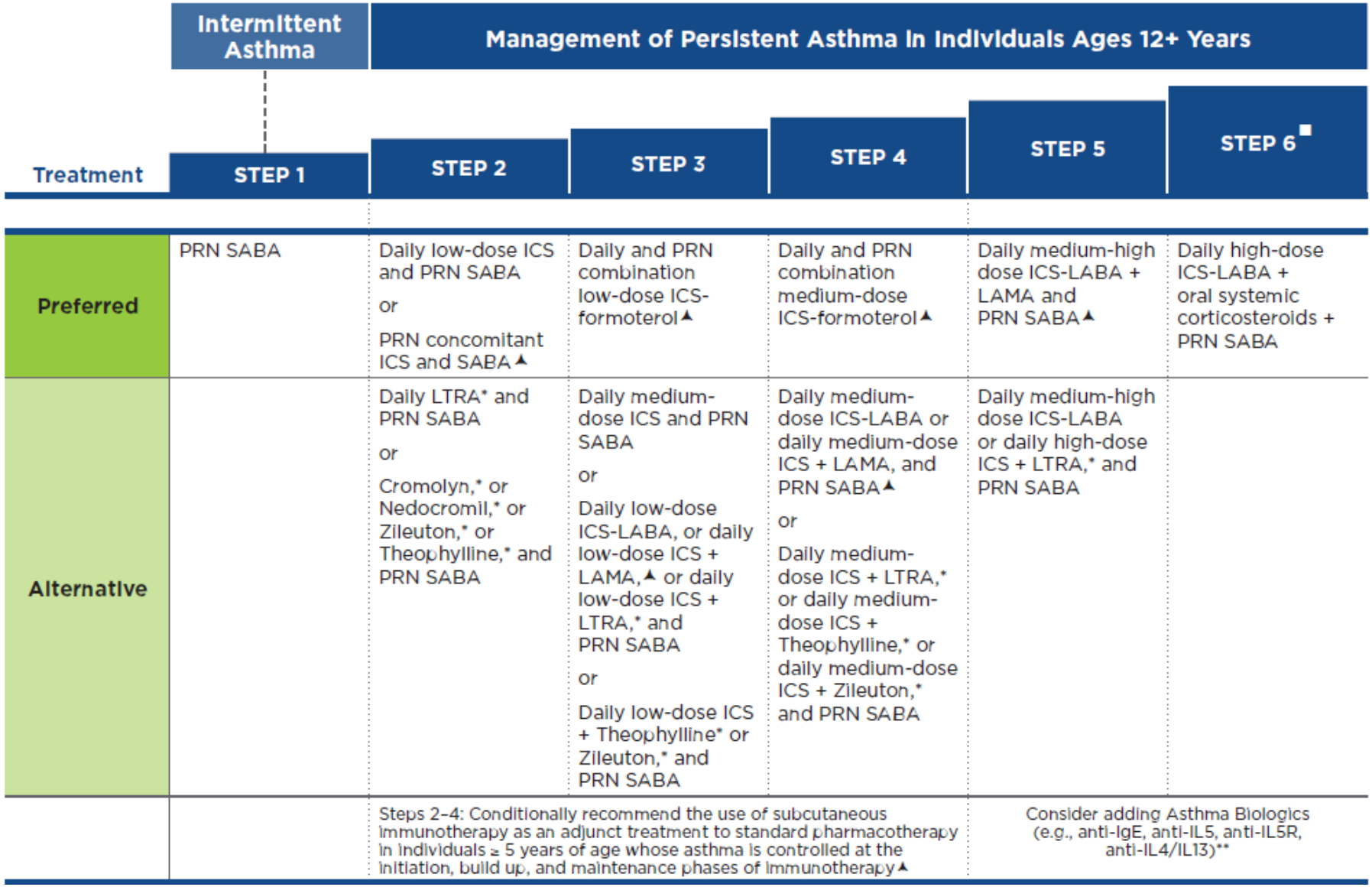
	Step 1	Step 2	Step 3	Step 4
Long-term management agents	ICS (low dose)	ICS (low to medium doses)	ICS (medium to high doses)	ICS (high dose)
Basic treatment	If the above agent cannot be used, use one of the following agents. • LTRA • Theophylline sustained-release preparation (unnecessary for rare symptoms)	If the above agent is ineffective, concomitantly use one of the following agents. • LABA (a compounding agent can be used)* • LAMA • LTRA • Theophylline sustained-release preparation	Concomitantly use one or more of the agents below. • LABA (a compounding agent can be used)* • LAMA • LTRA • Theophylline sustained-release preparation • Anti-IL-4Rα antibody	Concomitantly use two or more of the agents below. • LABA (a compounding agent can be used)* • LAMA • LTRA • Theophylline sustained-release preparation • Anti-IL-4Rα antibody • Anti-IgE antibody • Anti-IL-5 antibody • Anti-IL-5Rα antibody • Oral corticosteroid • Bronchial thermoplasty
Additional treatment				
Exacerbation treatment	Inhaled SABA	Inhaled SABA	Inhaled SABA	Inhaled SABA

* In patients treated with a combination of budesonide/formoterol as a controller, the agent should not be used beyond the recommended maximum per time and per day if it is used as a rescue; the recommended maximum is generally up to 8 inhalations/day. However, it can be used for up to 12 inhalations/day (for 3 days: budesonide, 1920 mg/day; formoterol 54 mg/day) temporarily. When more than 8 inhalations/day of budesonide/formoterol are needed, a physician should be consulted.

Inhaled corticosteroid, ICS; LTRA, leukotriene receptor antagonists; LABA, long-acting b2 agonist; SABA, short-acting b2 agonist; LAMA, long-acting muscarinic antagonist.

Yoichi Nakamura et al. *Allergology Int.* 2020;69:4:519-548

NAEPP guideline EPR-4 [1]



Treatment	Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 12+ Years				
	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6 ■
Preferred	PRN SABA	Daily low-dose ICS and PRN SABA or PRN concomitant ICS and SABA▲	Daily and PRN combination low-dose ICS-formoterol▲	Daily and PRN combination medium-dose ICS-formoterol▲	Daily medium-high dose ICS-LABA + LAMA and PRN SABA▲	Daily high-dose ICS-LABA + oral systemic corticosteroids + PRN SABA
Alternative		Daily LTRA* and PRN SABA or Cromolyn,* or Nedocromil,* or Zileuton,* or Theophylline,* and PRN SABA	Daily medium-dose ICS and PRN SABA or Daily low-dose ICS-LABA, or daily low-dose ICS + LAMA,▲ or daily low-dose ICS + LTRA,* and PRN SABA or Daily low-dose ICS + Theophylline* or Zileuton,* and PRN SABA	Daily medium-dose ICS-LABA or daily medium-dose ICS + LAMA, and PRN SABA▲ or Daily medium-dose ICS + LTRA,* or daily medium-dose ICS + Theophylline,* or daily medium-dose ICS + Zileuton,* and PRN SABA	Daily medium-high dose ICS-LABA or daily high-dose ICS + LTRA,* and PRN SABA	
		Steps 2–4: Conditionally recommend the use of subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy in individuals ≥ 5 years of age whose asthma is controlled at the initiation, build up, and maintenance phases of immunotherapy▲			Consider adding Asthma Biologics (e.g., anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13)**	

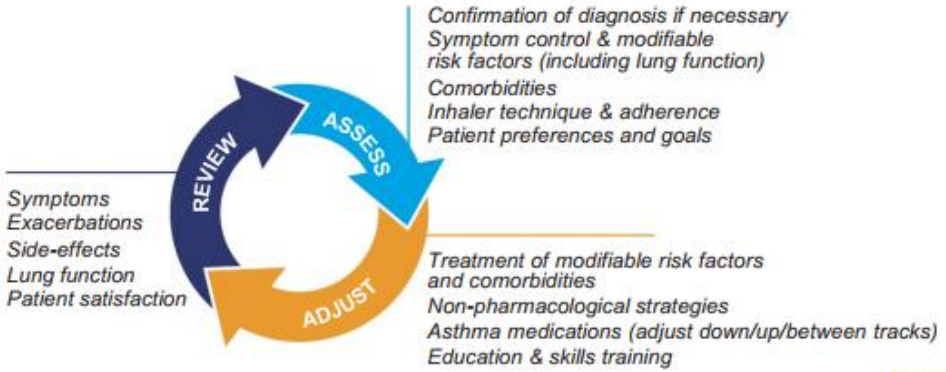
1. National Asthma Education and Prevention Program Coordinating Committee Expert Panel Report -4

2021 GINA Guideline

now shows 'two tracks' for asthma management based on evidence of outcome with the two reliever choices across asthma severity

Adults & adolescents 12+ years

Personalized asthma management
Assess, Adjust, Review
for individual patient needs



CONTROLLER and PREFERRED RELIEVER
(Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever

STEPS 1 – 2	STEP 3	STEP 4	STEP 5
As-needed low dose ICS-formoterol	Low dose maintenance ICS-formoterol	Medium dose maintenance ICS-formoterol	Add-on LAMA Refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R Consider high dose ICS-formoterol
RELIEVER: As-needed low-dose ICS-formoterol			

CONTROLLER and ALTERNATIVE RELIEVER
(Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller

STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Take ICS whenever SABA taken	Low dose maintenance ICS	Low dose maintenance ICS-LABA	Medium/high dose maintenance ICS-LABA	Add-on LAMA Refer for phenotypic assessment ± anti-IgE, anti-IL5/5R, anti-IL4R Consider high dose ICS-LABA
RELIEVER: As-needed short-acting β2-agonist				

Other controller options for either track

	Low dose ICS whenever SABA taken, or daily LTRA, or add HDM SLIT	*Medium dose ICS, or add LTRA, or add HDM SLIT*	*Add LAMA or LTRA, or switch to high dose ICS*	*Add azithromycin (adults) or LTRA; add low dose OCS but consider side-effects*

Global strategy for asthma management and prevention updated 2021

2021 GINA Guideline

‘Two tracks’ for asthma management

From Global Initiative for Asthma(GINA) What’s new in GINA 2021 ?

- For clarity, the GINA figure shows two ‘tracks’
  - **Track 1, with low dose ICS-FOR as the reliever, is the preferred approach**
  - **Track 2, with SABA as the reliever, is an alternative approach**

- Not distinguish between ‘intermittent’ and ‘mild persistent’ asthma

- To avoid confusion,

Severe asthma has been reworded that remains uncontrolled despite optimized treatment with high dose ICS-LABA without reference to GINA steps.

- Add on LAMA, Azithromycin, Biologics

What’s new in GINA 2021 ?
Accessed on https://ginasthma.org/wp-content/uploads/2021/05/Whats-new-in-GINA-2021_final_V2.pdf

Add-on lung-acting muscarinic antagonists (LAMA)

- Step 5 recommendations for add-on LAMA have been expanded to include combination ICS-LABA-LAMA, if asthma is persistently uncontrolled despite ICS-LABA
  - Add-on tiotropium in separate inhaler (ages ≥6 years)
  - Triple combinations (ages ≥ 18 years): beclometasone-formoterol-glycopyrronium; fluticasone furoate-vilanterol-umeclidinium; mometasone-indacaterol-glycopyrronium
- Lung function:
  - Adding LAMA to medium or high dose ICS-LABA modestly improves lung function (Evidence A) but not symptoms
- Severe exacerbations
  - In some studies, add-on LAMA modestly increased the time to severe exacerbation requiring OCS (Evidence B)
  - For patients with exacerbations, it is important to ensure that the patient receives sufficient ICS, i.e. at least medium dose ICS-LABA, before considering adding a LAMA

ICS: inhaled corticosteroids; LABA: long-acting beta$_2$-agonist; LAMA: long-acting muscarinic antagonist; OCS: oral corticosteroids

2. LAMA as an add-on therapeutic option: Synergism

Muscarinic antagonists-New LAMAs

Table 1
Potency, onset and duration of action of muscarinic antagonists in inhibiting EFS-induced contraction of human bronchi (n = 6–7).

	Potency	Onset of action (min)			Offset of action (min)	
	pIC_{50}	nM	$T_{1/2}$ (min)	T_{max}	$T_{1/2}$ (min)	% inhibition at 9 h
tiotropium **Spiriva®**	9.75 ± 0.05	1	12 ± 3	34 ± 5	> 540	70 ± 8
glycopyrronium **Seebri®**	9.37 ± 0.12	3	14 ± 3	36 ± 6	129 ± 40	26 ± 4
ipratropium **Atrovent®**	9.00 ± 0.09	10	7 ± 1	30 ± 7	59 ± 27	33 ± 13
umeclidinium **Incruse®**	8.88 ± 0.09	10	9 ± 2	55 ± 3	> 540	75 ± 3
aclidinium **Eklira®**	8.61 ± 0.11	30	10 ± 3	47 ± 3	(200, > 540)	47 ± 7

Data are quoted as the mean (± SEM) of n independent experiments. pIC_{50} are the values after the first hour of incubation (before washout). $T_{1/2}$: time to achieve 50% inhibition or recovery of EFS-induced contraction. Tmax: time to achieve maximal inhibition. The onset and offset times were determined for 1 nM tiotropium, 3 nM glycopyrronium, 10 nM ipratropium, 10 nM umeclidinium and 30 nM aclinidium.

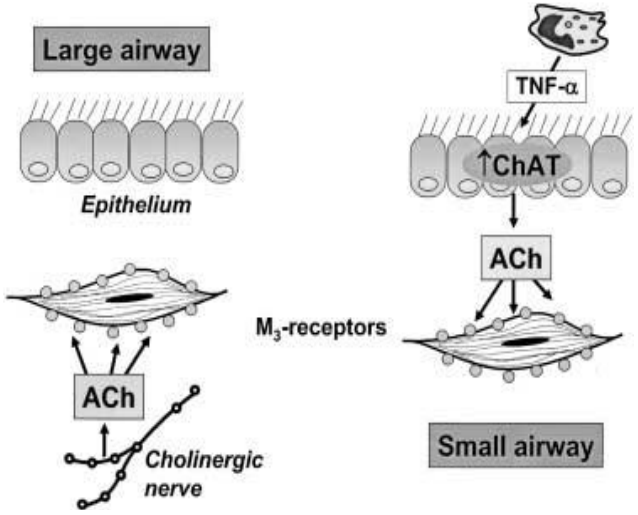
All the LAMAs : a long dissociation time at the hM3R and high tissue partitioning.
: differ slightly in their onset of action
: differ markedly in their duration of action and potency

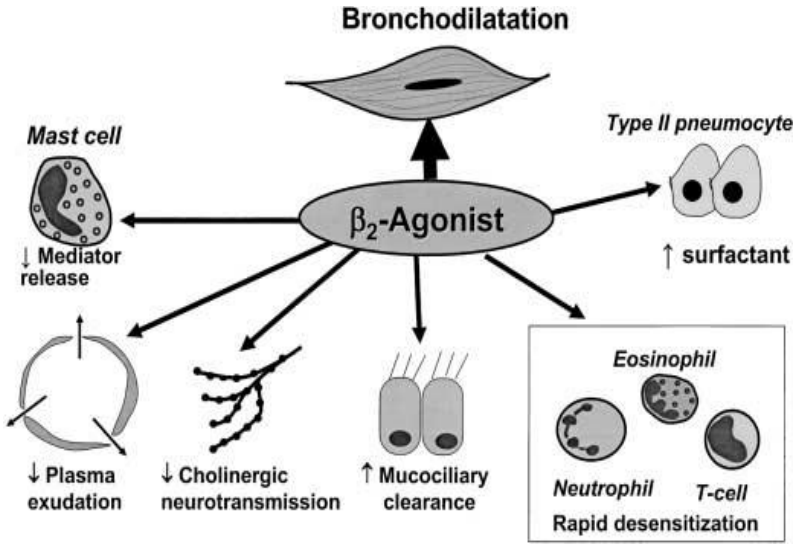
Pulmonary Pharmacology & Therapeutics 49 (2018) 46–53

LABA vs. LAMA in asthma

- **LABA**s are by far the most effective bronchodilators in **asthma**
- **LAMA**s are the most effective class of bronchodilator in patients with **COPD**

    - In asthma, anticholinergics are considerably less effective as bronchodilators than B2-agonists, because they block only the cholinergic component of bronchoconstriction, which is usually minimal compared to the direct constrictor effects of mediators, such as cys-LTs.



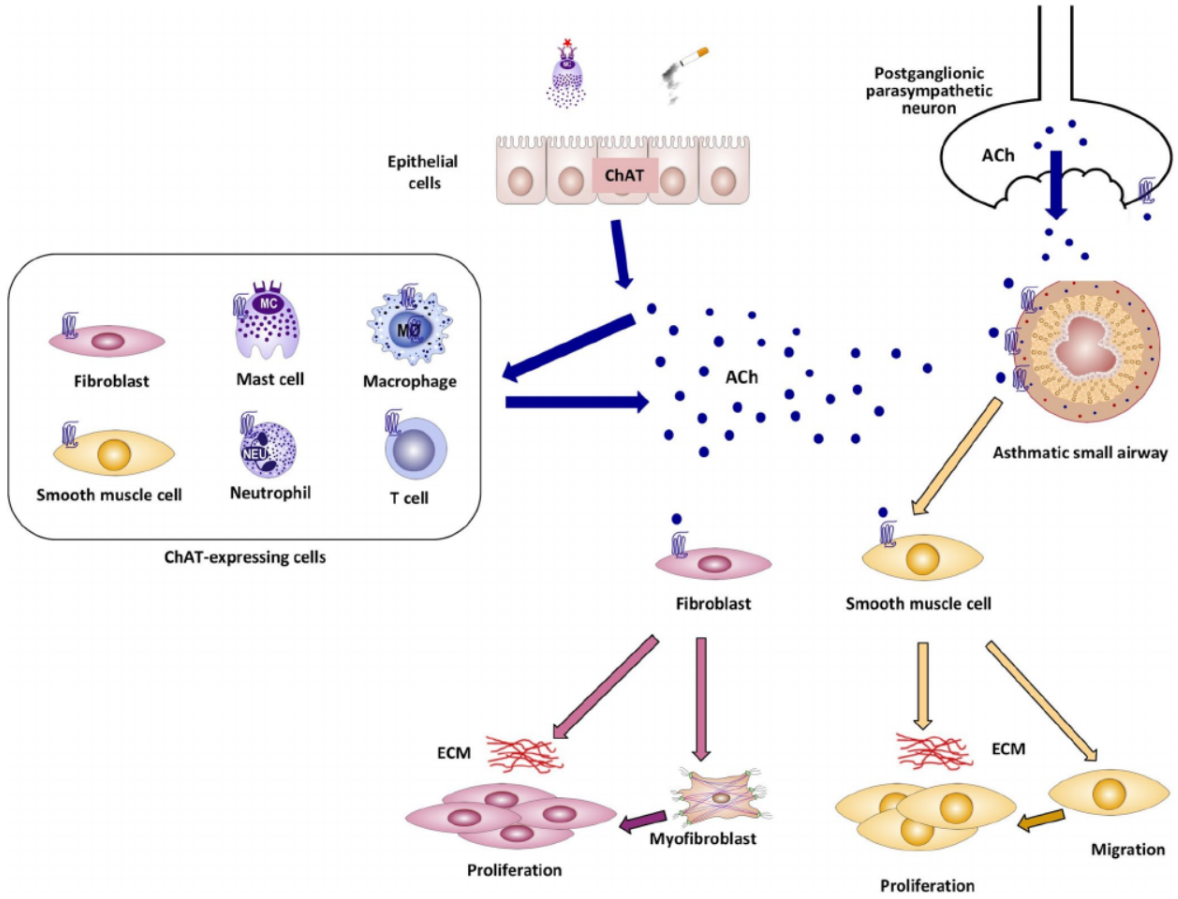


Proc Am Thorac Soc Vol 1. pp 345–351, 2004

LABA vs. LAMA in asthma

Cholinergic innervation in human peripheral airways

Structure	Branch generation	Distribution of mAChR subtypes and β-AR subtypes (abundance, fmol·mg^{-1} of protein)			
		M_2 mAChR	M_3 mAChR	β_1-AR	β_2-AR
Trachea	0				
Primary bronchi	1				
Secondary bronchi	2				
Tertiary bronchi	3	47	48	0	50
Small bronchi	4				
Bronchioles	5-7				
Terminal bronchioles	8-16	11	28	0	85
Respiratory bronchioles	17-19	27	0	98	205
Alveolar ducts and sacs	20-23				



Allergy. 2021;76:1990–2001

LABA vs. LAMA in asthma

TALC

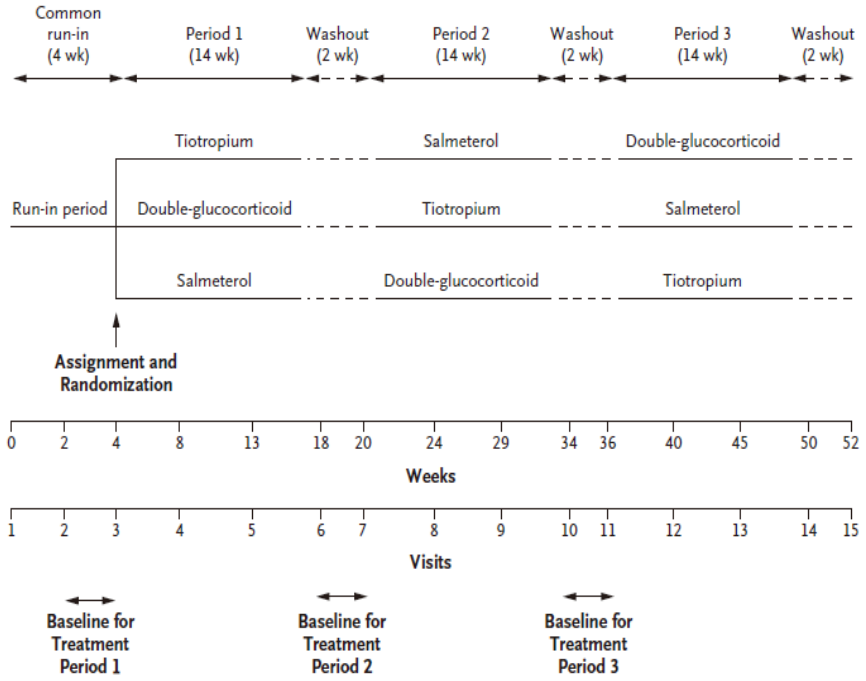
- **A three-way, double-blind, triple-dummy crossover trial (14 week/Period)**
- **Moderate asthma (n=210)**
- Tio 5, Salmeterol, beclomethasone Double

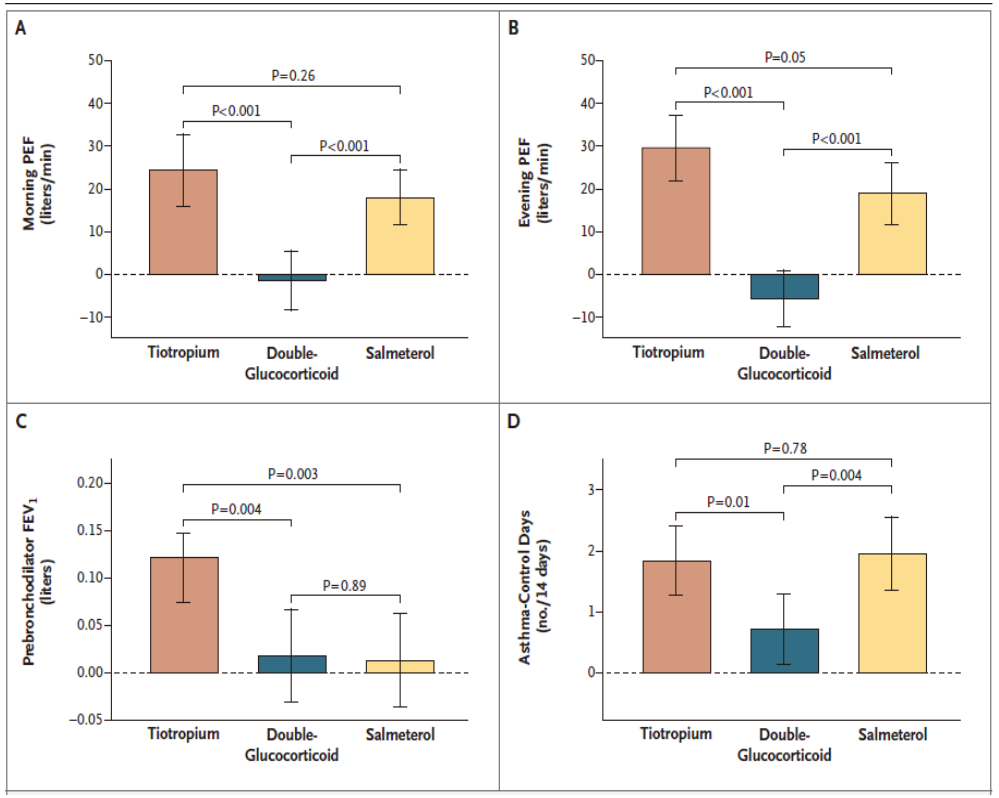
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tiotropium Bromide Step-Up Therapy for Adults with Uncontrolled Asthma

Stephen P. Peters, M.D., Ph.D., Susan J. Kunselman, M.A., Nikolina Icitovic, M.A.S., Wendy C. Moore, M.D., Rodolfo Pascual, M.D., Bill T. Ameredes, Ph.D., Homer A. Boushey, M.D., William J. Calhoun, M.D., Mario Castro, M.D., Reuben M. Cherniack, M.D., Timothy Craig, D.O.,





N Engl J Med 2010;363:1715-26.

Its effects appeared to be equivalent to those with the addition of salmeterol.

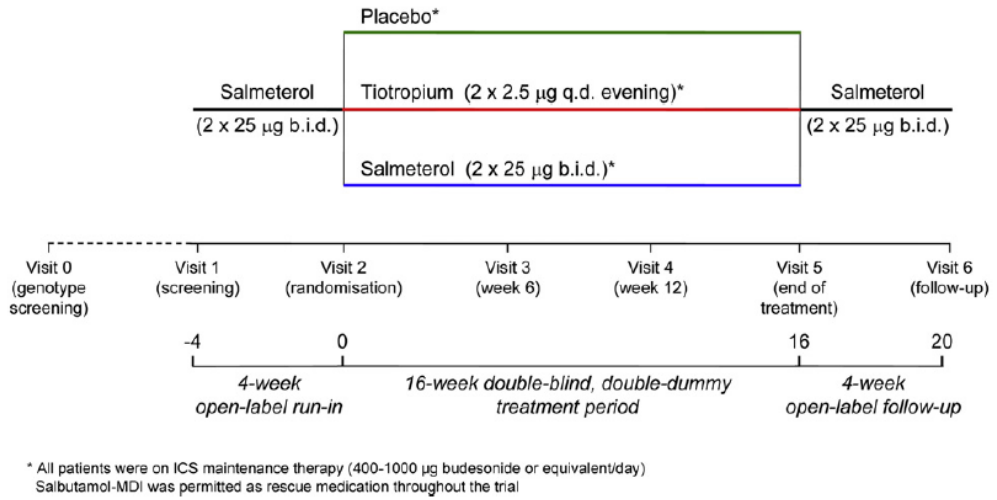
LABA vs. LAMA in asthma

NCT00350207

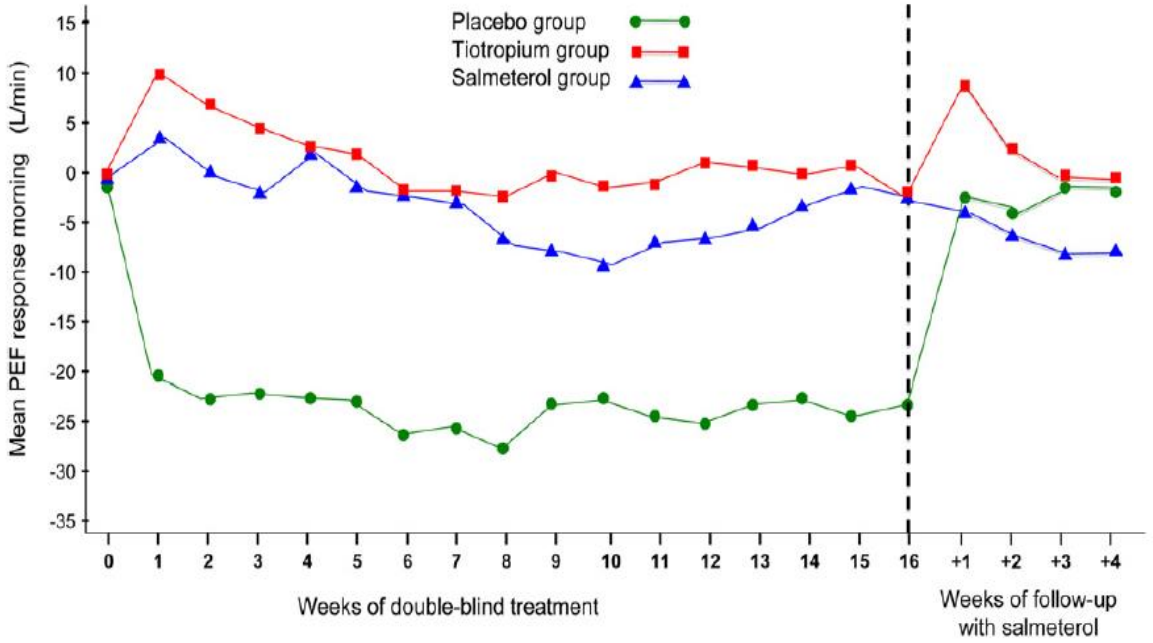
Tiotropium is noninferior to salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma

Eric D. Bateman, MD,[a] Oliver Kornmann, MD,[b] Peter Schmidt, PhD,[c] Anna Pivovarova, DiplStat,[c] Michael Engel, MD,[c] and Leonardo M. Fabbri, MD[d] *Cape Town, South Africa, Frankfurt and Biberach, Germany, and Modena, Italy*

- **Double-blind, double-dummy, placebo-controlled trial (16 weeks)**
- **Moderate asthma**
- Tio (n=128) Salmeterol (n=134) Placebo (n=126)



* All patients were on ICS maintenance therapy (400-1000 µg budesonide or equivalent/day)
Salbutamol-MDI was permitted as rescue medication throughout the trial



Numbers of patients

Double-blind treatment period:	Placebo n=125	Tiotropium n=128	Salmeterol n=134
Follow-up period:	Placebo n=118	Tiotropium n=121	Salmeterol n=127

Tiotropium was noninferior to salmeterol in the primary analysis based on the change in mean weekly morning PEF from baseline to the last week of treatment

J Allergy Clin Immunol 2011;128:315-22

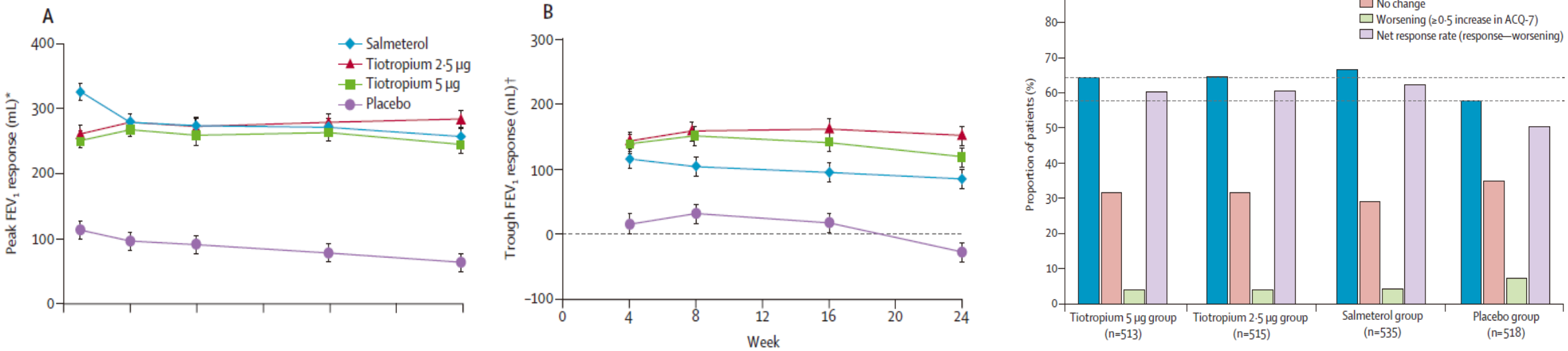
LABA vs. LAMA in asthma

MezzoTinA

Tiotropium or salmeterol as add-on therapy to inhaled corticosteroids for patients with moderate symptomatic asthma: two replicate, double-blind, placebo-controlled, parallel-group, active-comparator, randomised trials

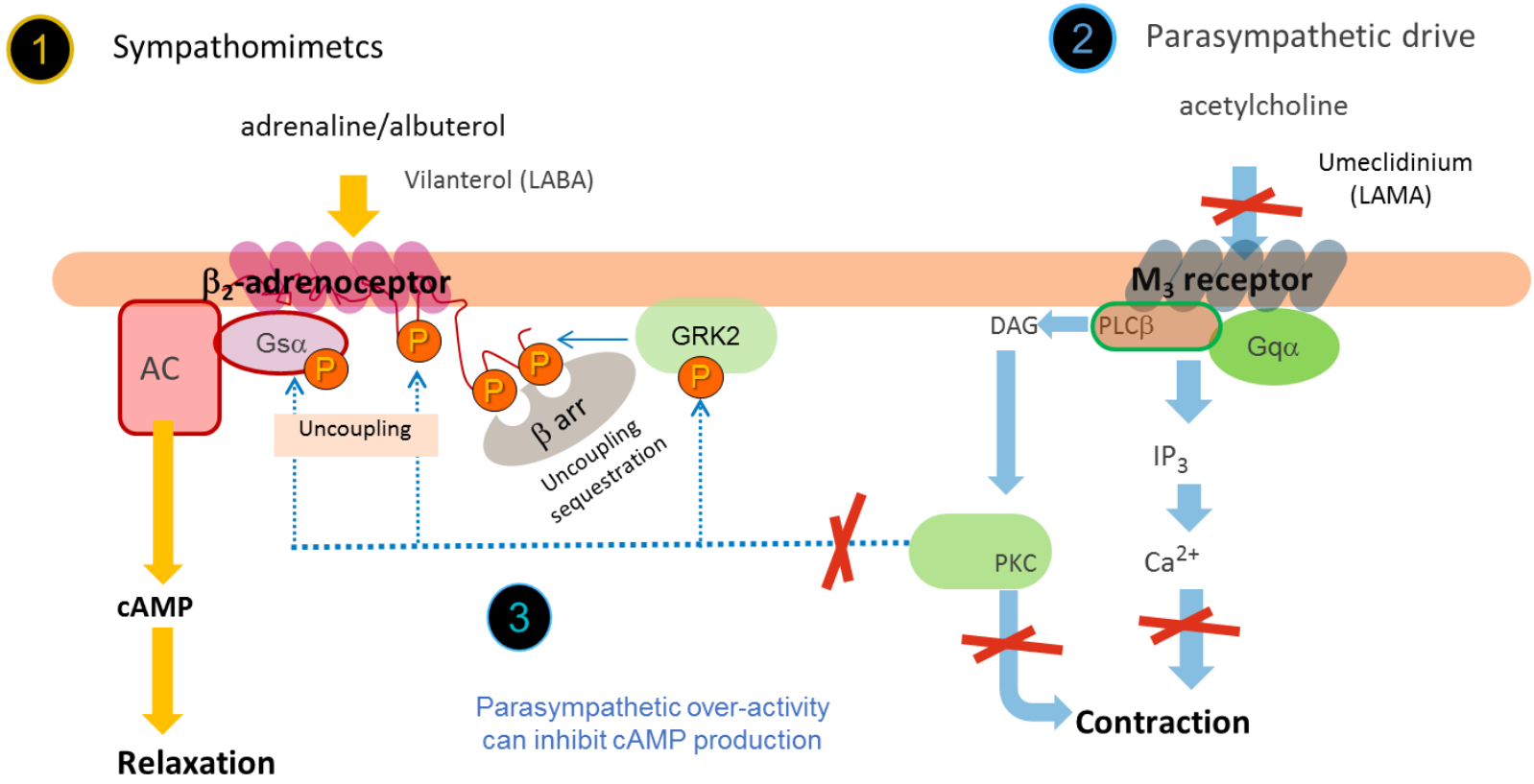
*Huib A M Kerstjens, Thomas B Casale, Eugene R Bleecker, Eli O Meltzer, Emilio Pizzichini, Olaf Schmidt, Michael Engel, Loek Bour, Cynthia B Verkleij, Petra Moroni-Zentgraf, Eric D Bateman**

- **Double blind, randomized, placebo-controlled, parallel group, replicate (24 week)**
- **Moderate asthma,** At least medium dose ICS
- Tio 5 ug (n=519) Tio 2.5ug (n=520) Salmeterol (n=541) Placebo (n=523)



Lancet Respir Med 2015;3: 367–76

The pathways of dual bronchodilation: LABA-LAMA synergism

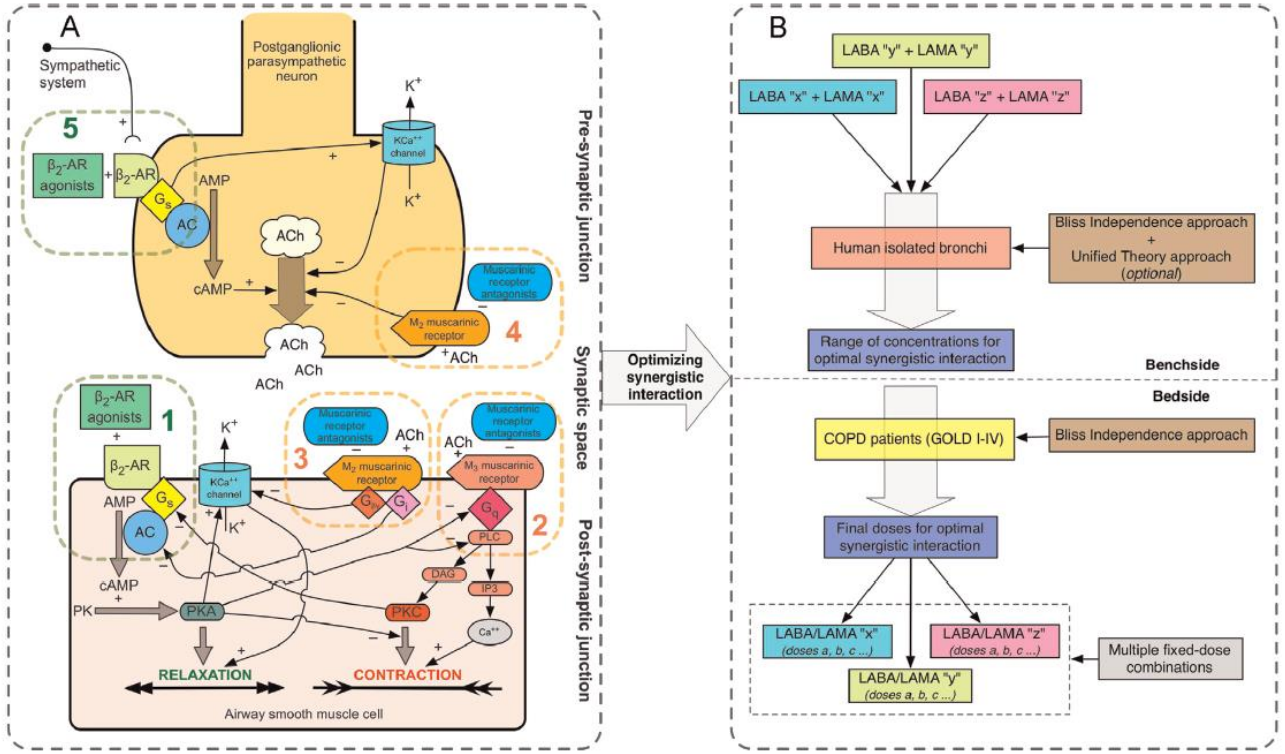


VI monotherapy is an unlicensed investigational medicinal product

Adapted from Meurs H et al Pulmonary Pharmacology & Therapeutics (2013)

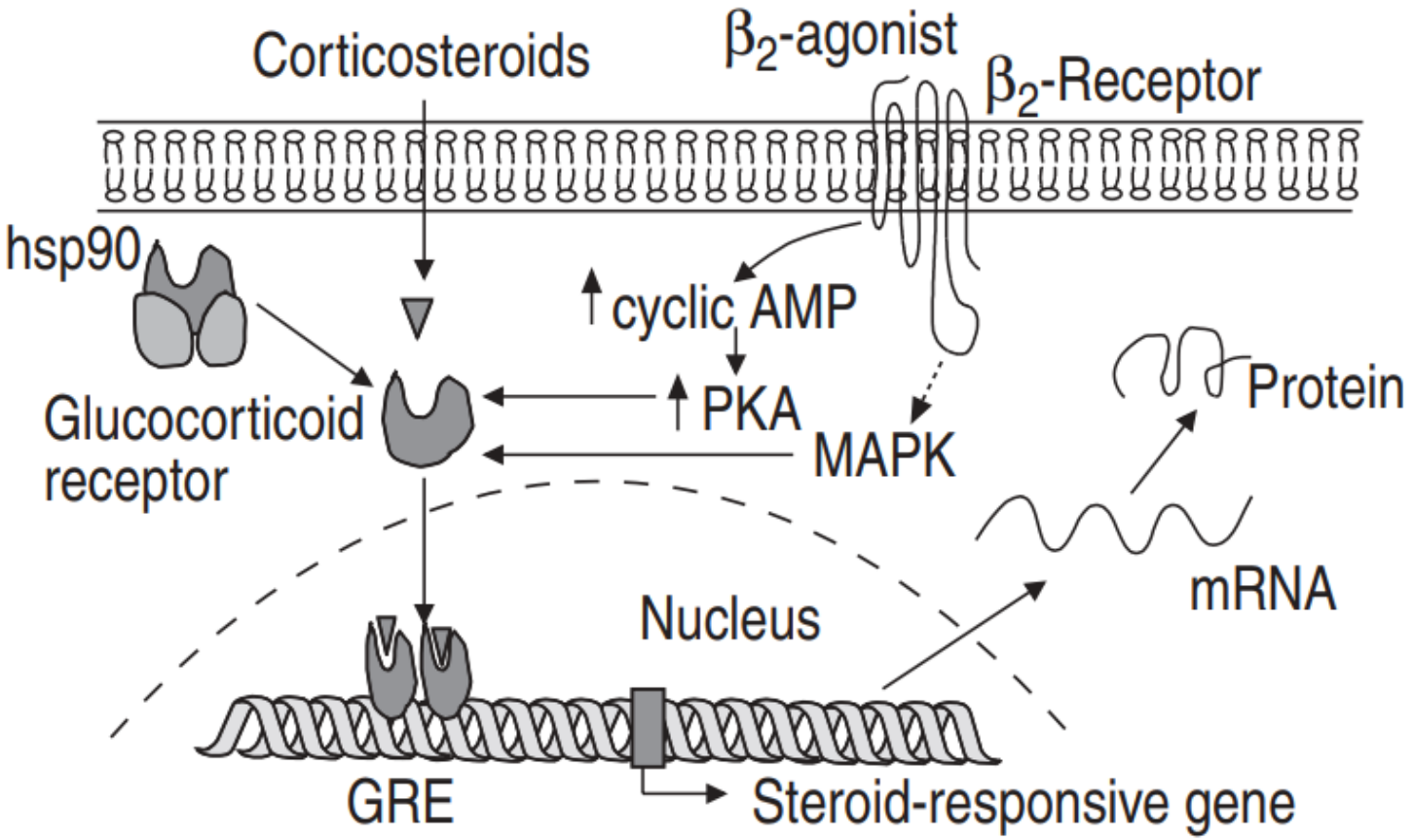
Pharmacologic rationale for dual bronchodilation

- *β2 agonist can reduce the release of acetylcholine in pre-junctional cholinergic nerves*
- *Crosstalk between muscarinic receptors and β2 -adrenoceptors, causing functional antagonism at the level of the airway smooth muscle itself*
- *The anti-muscarinic agent can suppress mucus/fluid secretions*



Pharmacol Rev. 2012;64:450–504.; Pulm Pharmacol Ther. 2010;23:257–267.; Br J Pharmacol. 2011;163:4–17.; Curr Opin Pharmacol. 2013;13:316–323.; . Pulm Pharmacol Ther. 2013;26:145–155; EuropeanJournalofPharmacology761(2015)168–173

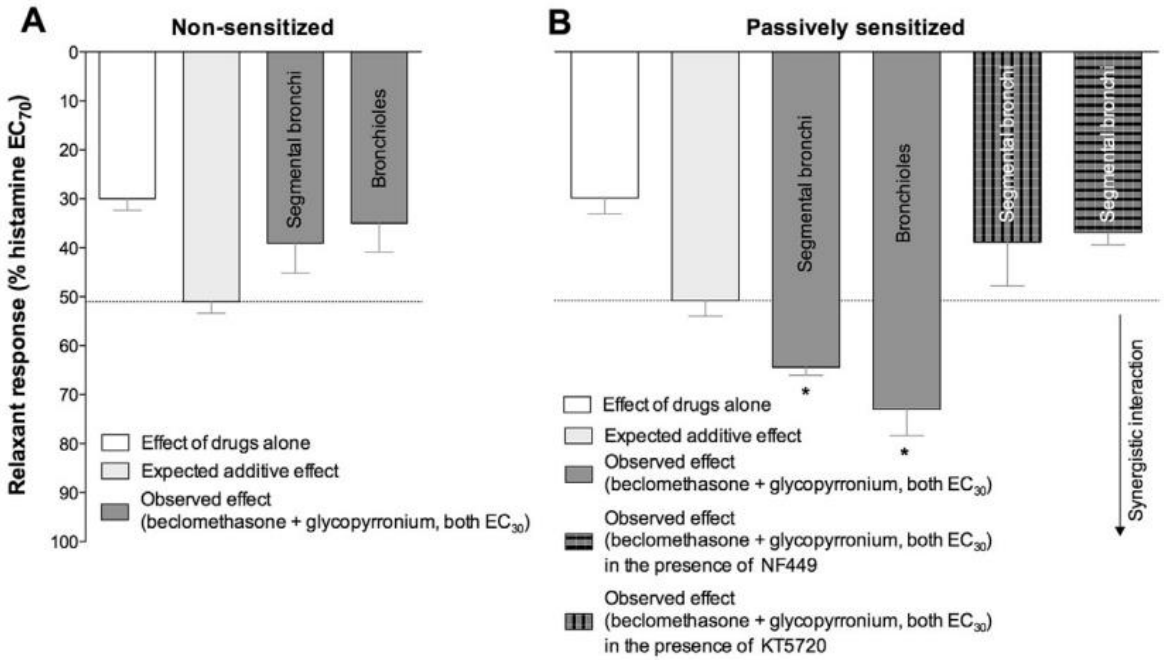
The pathways of ICS-LABA synergism



Eur Respir J 2002; 19: 182–191

Experimental evidence for ICS-LAMA synergism

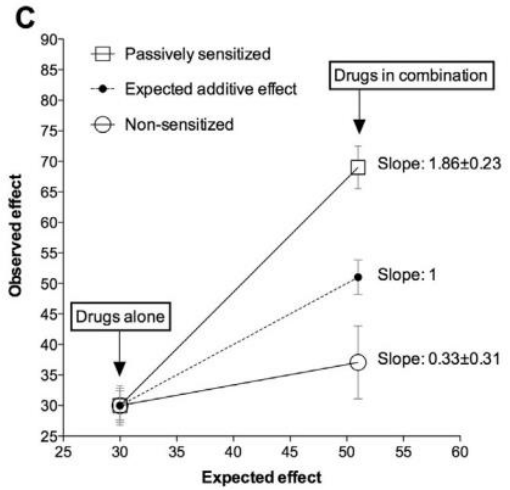
- The pharmacological mechanisms of the interactions between mAChR antagonists and ICS are **not yet clear.**

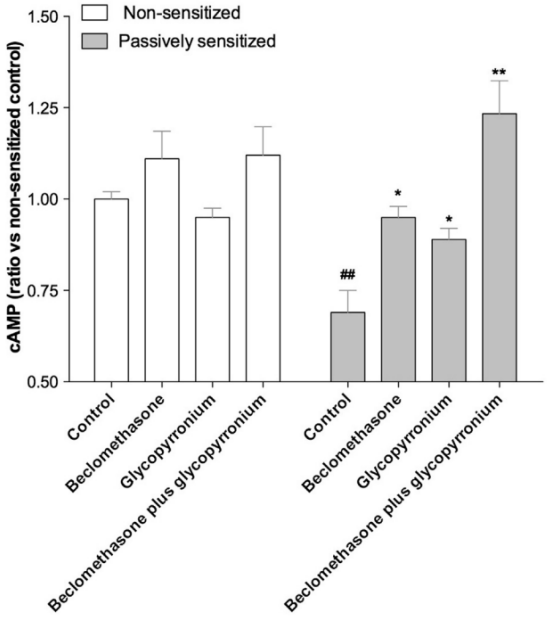


Interaction between corticosteroids and muscarinic antagonists in human airways

Mario Cazzola [a, b, c], Luigino Calzetta [b, *], Paola Rogliani [a, c], Ermanno Puxeddu [c], Francesco Facciolo [d], Maria Gabriella Matera [e]

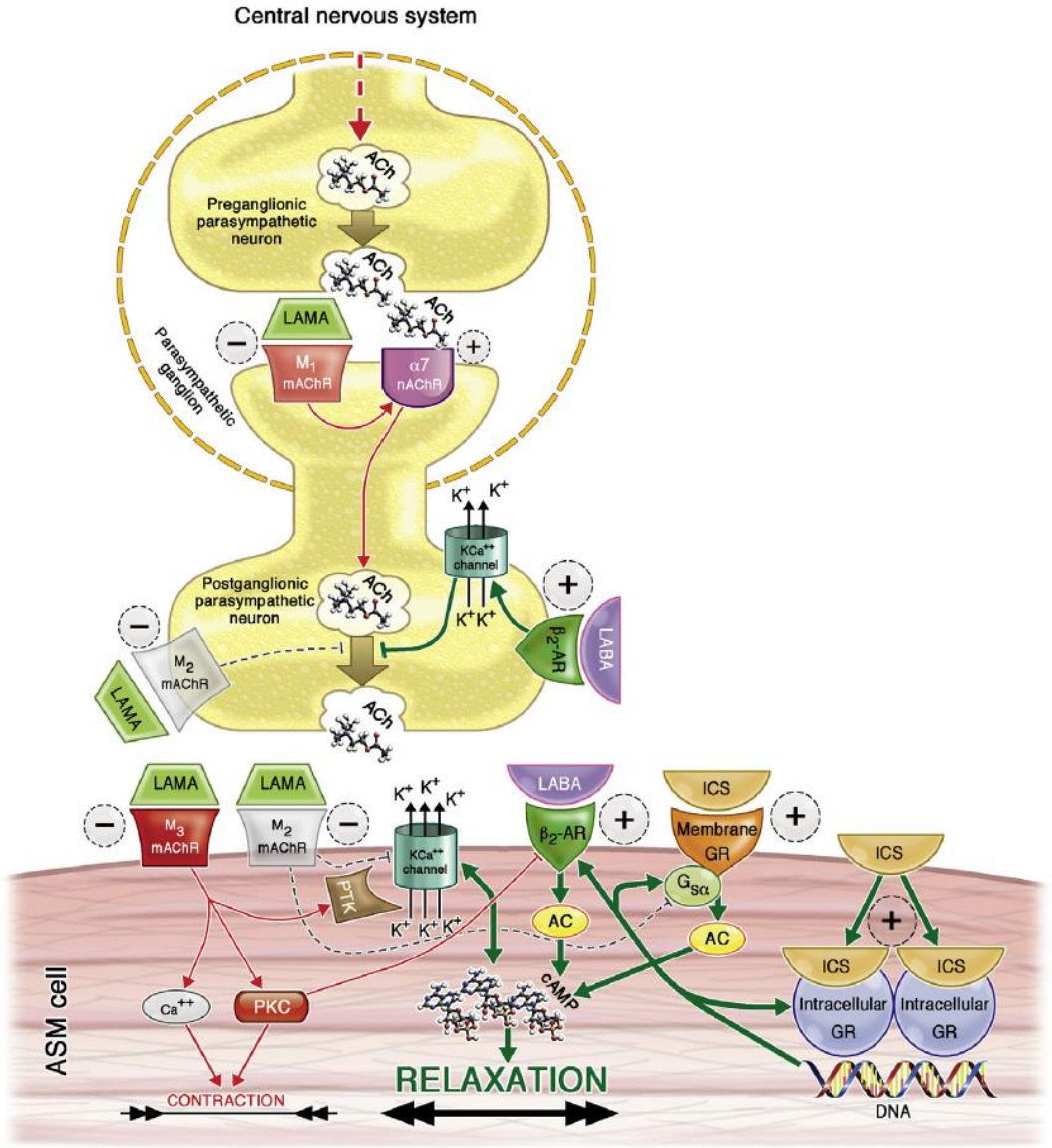
[a] University of Rome Tor Vergata, Department of Systems Medicine, Chair of Respiratory Medicine, Rome, Italy
[b] University of Rome Tor Vergata, Department of Systems Medicine, Respiratory Pharmacology Research Unit, Rome, Italy
[c] University Hospital Tor Vergata, Division of Respiratory Medicine, Rome, Italy
[d] Regina Elena National Cancer Institute, Thoracic Surgery Unit, Rome, Italy
[e] Second University of Naples, Department of Experimental Medicine, Unit of Pharmacology, Naples, Italy





Pharmacological Reviews January 2020, 72 (1) 218-252; Pulm Pharmacol Ther. 2016 Feb;36:1-9

The pharmacological optimization of bronchodilation and the rationale for triple therapy (ICS-LABA-LAMA)



Pharmacological Reviews January 2020, 72 (1) 218-252;
J Allergy Clin Immunol 2020;146:1288-91.

3. Add-on Tiotropium therapy in uncontrolled asthma

Clinical trials of tiotropium in patients with asthma (1)

Clinical trial	Study design	Duration	Patient population	Treatment arms*	Key endpoints/ objectives
Adults (18–75 years old)					
PrimoTinA-asthma® 1 and 2 (NCT00772538/ NCT00776984) 2012[7]	Two replicate double-blind, randomized, placebo-controlled, parallel group, replicate studies	48 weeks	Symptomatic severe asthma receiving at least high-dose ICSs and LABA maintenance	• Tio 5 µg ($n = 456$) • Placebo ($n = 456$)	• Peak $FEV_{1(0–3\ h)}$ • Trough FEV_1 • Time to first severe exacerbation • Safety†
MezzoTinA-asthma® 1 and 2 (NCT01172808/ NCT01172821) 2015[8]	Two replicate double-blind, randomized, double-dummy, placebo-controlled, parallel group, replicate studies	24 weeks	Symptomatic moderate asthma receiving at least medium-dose ICSs	• Tio 5 µg ($n = 517$) • Tio 2.5 µg ($n = 519$) • Salmeterol ($n = 541$) • Placebo ($n = 523$)	• Peak $FEV_{1(0–3\ h)}$ • Trough FEV_1 • ACQ-7 responder rate • Safety†
GraziaTinA-asthma® (NCT01316380) 2016[9]	Placebo-controlled, randomized, parallel-group study	12 weeks	Symptomatic mild-to-moderate asthma receiving low-to-medium-dose ICSs	• Tio 5 µg ($n = 155$) • Tio 2.5 µg ($n = 154$) • Placebo ($n = 155$)	• Peak $FEV_{1(0–3\ h)}$ • Safety†
CadenTinA-asthma® (NCT01340209) 2015[10]	Double-blind, randomized, placebo-controlled, parallel-group study	52 weeks	Symptomatic moderate-to-severe asthma receiving at least medium-dose ICSs	• Tio 5 µg ($n = 114$) • Tio 2.5 µg ($n = 114$) • Placebo ($n = 57$)	• Safety†

Ther Adv Respir Dis 2019, Vol. 13: 1–16.

Clinical trials of tiotropium in patients with asthma (2)

Adolescents (12–17 years old)					
PensieTinA-asthma® (NCT01277523) 2017[11]	Double-blind, randomized, parallel-group study	12 weeks	Symptomatic severe asthma receiving high-dose ICSs plus ⩾1 controller or medium-dose ICSs plus ⩾2 controllers	• Tio 5 µg (n = 130) • Tio 2.5 µg (n = 127) • Placebo (n = 135)	• Peak $FEV_{1(0–3\ h)}$ • Safety†
RubaTinA-asthma® (NCT01257230) 2016[12]	Double-blind, randomized, placebo-controlled, parallel-group study	48 weeks	Symptomatic moderate asthma receiving at least medium-dose ICSs	• Tio 5 µg (n = 134) • Tio 2.5 µg (n = 125) • Placebo (n = 138)	• Peak $FEV_{1(0–3\ h)}$ • Safety†
Children (6–11 years old)					
VivaTinA-asthma® (NCT01634152) 2017[13]	Double-blind, randomized, placebo-controlled, parallel-group study	12 weeks	Symptomatic severe asthma receiving high-dose ICSs + ⩾1 controller or medium-dose ICSs with ⩾2 controllers	• Tio 5 µg (n = 130) • Tio 2.5 µg (n = 136) • Placebo (n = 134)	• Peak $FEV_{1(0–3\ h)}$ • Safety†
CanoTinA-asthma® (NCT01634139) 2018[14]	Double-blind, randomized, placebo-controlled, parallel-group study	48 weeks	Symptomatic moderate asthma receiving at least medium-dose ICSs	• Tio 5 µg (n = 135) • Tio 2.5 µg (n = 135) • Placebo (n = 131)	• Peak $FEV_{1(0–3\ h)}$ • Safety†
Children (1–5 years old)					
NinoTinA-asthma® (NCT01634113) 2018[15]	Double-blind, randomized, placebo-controlled, parallel-group study	12 weeks	Persistent asthmatic symptoms for ⩾6 months receiving at least stable-dose ICSs	• Tio 5 µg (n = 31) • Tio 2.5 µg (n = 36) • Placebo (n = 34)	• Safety†

Ther Adv Respir Dis 2019, Vol. 13: 1–16.

Add-on Tiotropium to ICS-LABA in asthma

Primo TinA

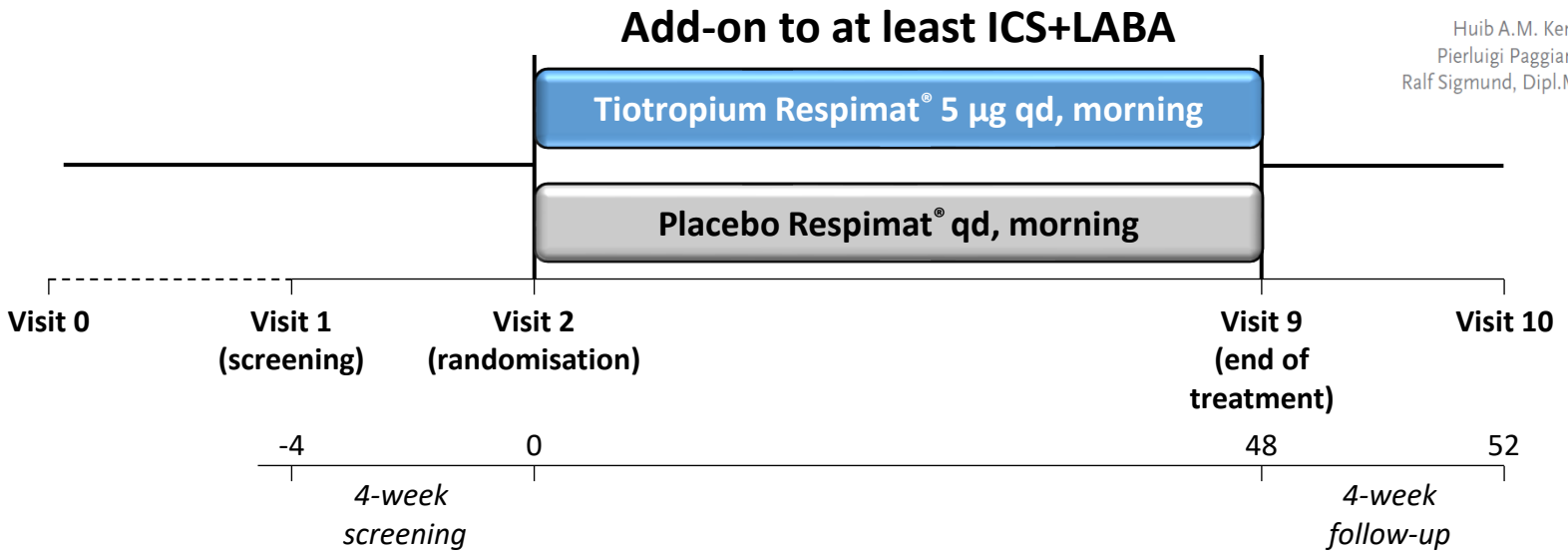
Study design: double-blind, randomised, placebo-controlled, parallel-group (twin trials)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tiotropium in Asthma Poorly Controlled with Standard Combination Therapy

Huib A.M. Kerstjens, M.D., Michael Engel, M.D., Ronald Dahl, M.D., Pierluigi Paggiaro, M.D., Ekkehard Beck, M.D., Mark Vandewalker, M.D., Ralf Sigmund, Dipl.Math., Wolfgang Seibold, M.D., Petra Moroni-Zentgraf, M.D., and Eric D. Bateman, M.D.



Three co-primary endpoints:
hierarchical testing

1. FEV_1 peak (0-3 h) after 24 weeks
2. FEV_1 trough after 24 weeks
3. Time to first severe asthma exacerbation in pooled* analysis after 48 weeks

All patients at least on ICS maintenance therapy (≥800 µg budesonide or equivalent/day)+LABA

148 centres, 5 continents

Kerstjens et al. *NEJM* 2012;367:1198-1207.
FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; qd, once daily
* Pre-specified dataset of trial 1 + trial 2

Main inclusion criteria
Primo TinA

- **Asthma diagnosis**
  - Asthma diagnosed at age <40 years, documented by BHR, PEF variability, or SABA or OCS response
  - 5-year history of asthma
  - 18–75 years
  - Never-smoker or ex-smoker ≥1 year cessation and <10 pack-years

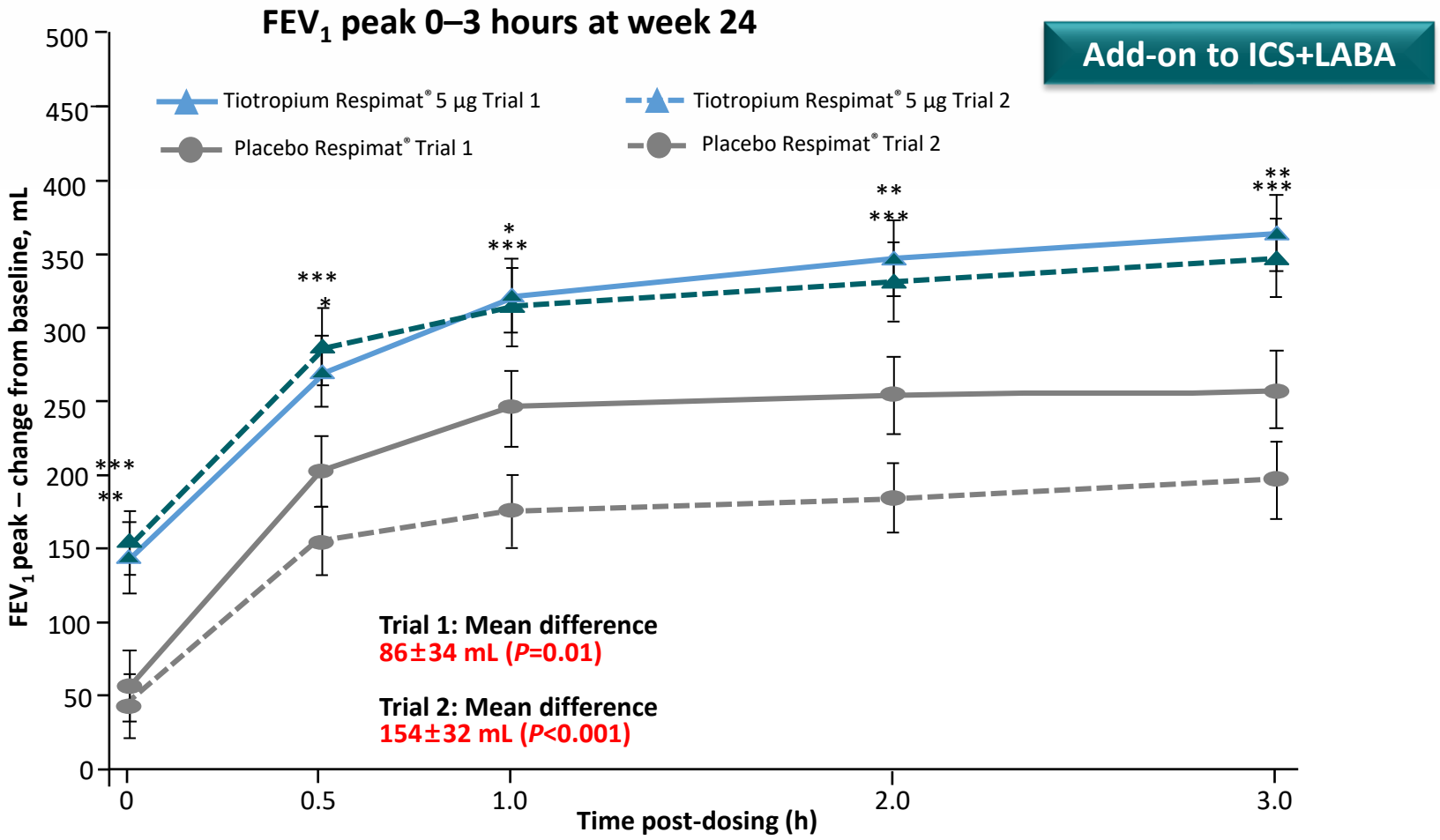
- **Symptomatic asthma**
  - Uncontrolled despite ICS+LABA and potential other controllers
    - Mandatory: high-dose ICS (≥800 µg budesonide equivalent)+LABA
    - Permitted: stable theophylline, leukotriene modifiers, omalizumab, oral steroids (≤5 mg/day)
    - ACQ ≥1.5 at screening and baseline visit

  Lung function
    - Post-bronchodilator FEV_1 ≤80% predicted; FEV_1/FVC ≤70% at screening

  Exacerbations
    - At least one severe asthma exacerbation in previous year treated with systemic steroids

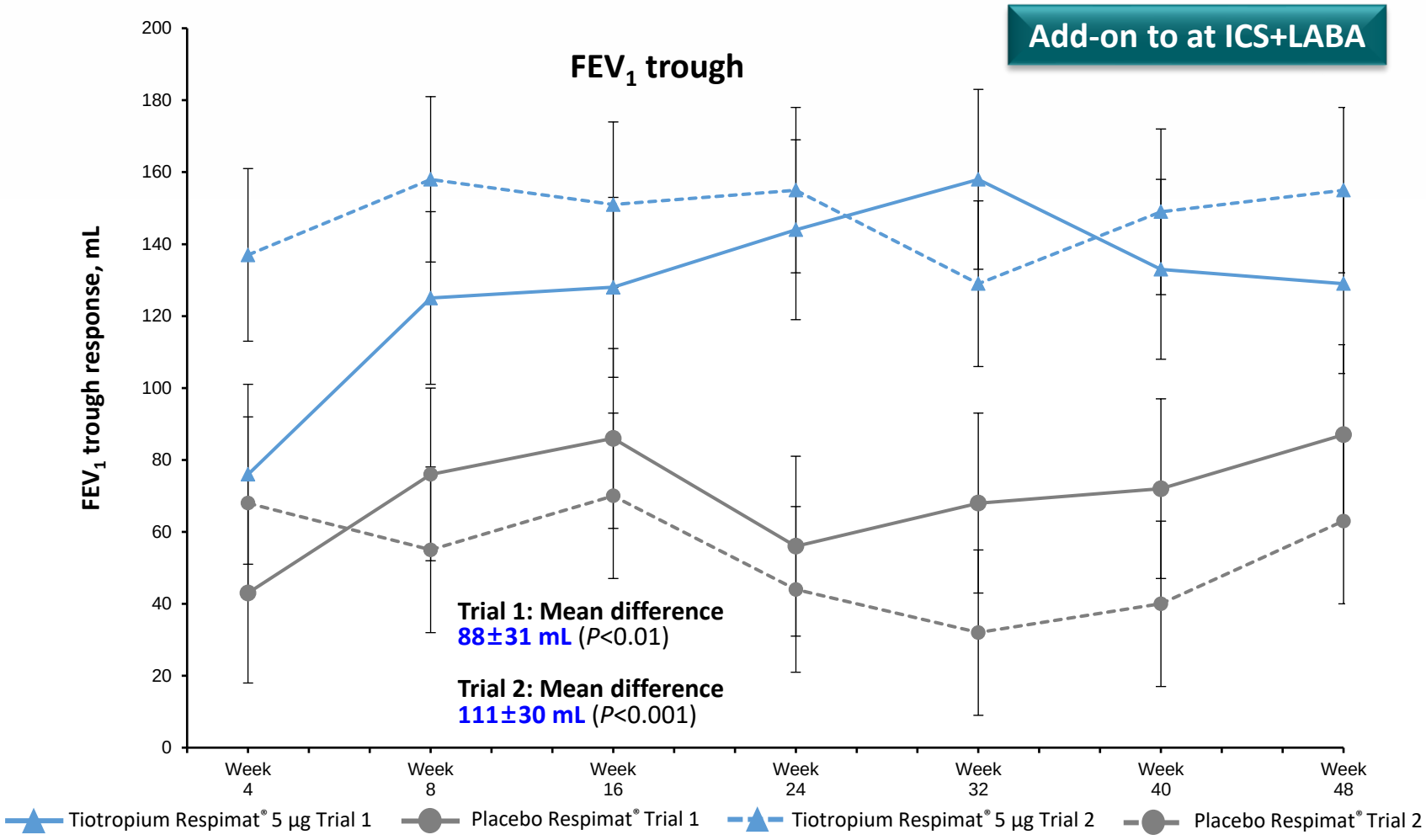
Kerstjens et al. *NEJM* 2012;367:1198-1207.
ACQ, asthma control questionnaire; BHR, bronchial hyper-responsiveness; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; OCS, oral corticosteroids; PEF, peak flow; SABA, short-acting β_2-agonist

Tiotropium Respimat® was associated with a significant improvement in FEV1 peak in Primo TinA



- Kerstjens H, et al. *N Engl J Med* 2012;367:1198–1207.
FEV$_1$, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist.
*P<0.05; **P<0.01; ***P<0.0001. Error bars represent standard errors

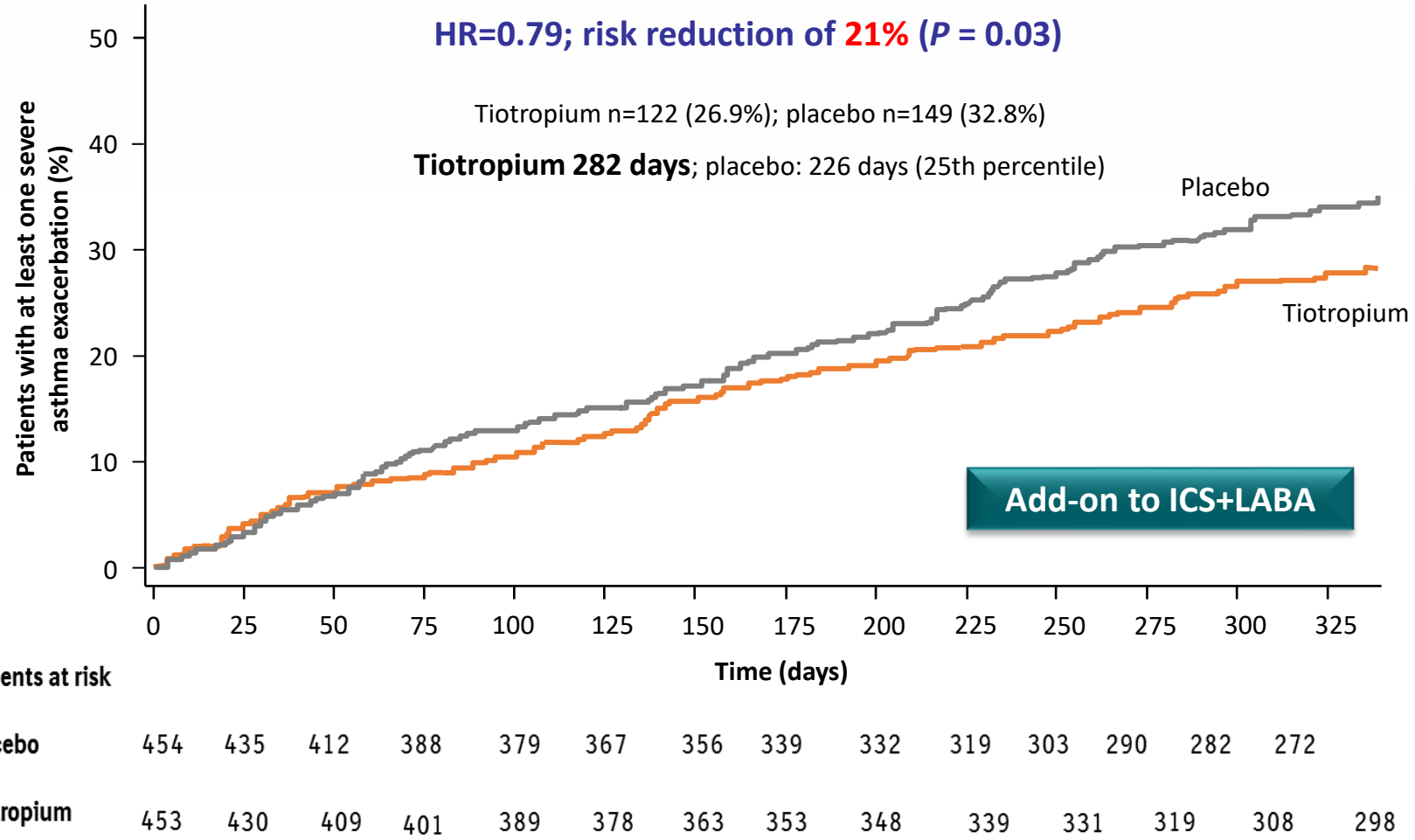
Significant lung function improvement in FEV_1 trough in Primo TinA



Kerstjens et al. *NEJM* 2012;367:1198-1207.

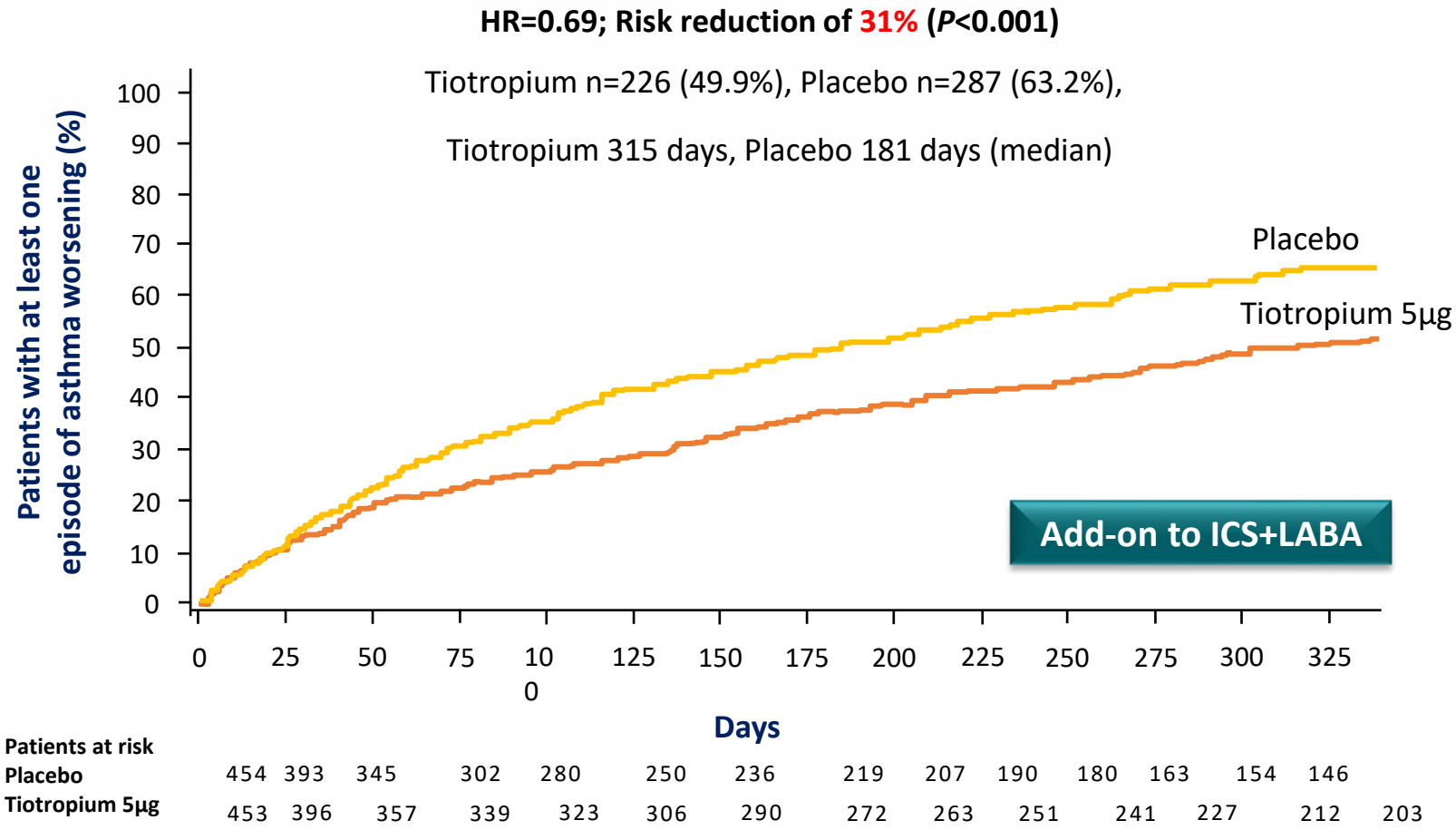
*P<0.05; **P<0.01; ***P<0.0001. Error bars represent standard errors

Severe asthma exacerbations in Primo TinA



Kerstjens et al. *NEJM* 2012;367:1198-1207.

Episodes of asthma worsening in Primo TinA



Kerstjens et al. *NEJM* 2012;367:1198-1207.

Adverse events: Overall summary- Primo TinA

	Tiotropium Respimat® n (%)	Placebo Respimat® n (%)
Number of patients	456 (100.0)	456 (100.0)
Total with any adverse event	335 (73.5)	366 (80.3)
Drug-related adverse event as defined by Investigator	26 (5.7)	21 (4.6)
Serious adverse event	37 (8.1)	40 (8.8)

No deaths occurred.

Kerstjens et al. *NEJM* 2012;367:1198-1207.
AE, adverse event; SAE, serious adverse event
ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist

Serious adverse events: Overall summary- Primo TinA

	Tiotropium Respimat® 5 µg, n (%)	Placebo Respimat® n (%)
Patients with serious AEs	37 (8.1)	40 (8.8)
Fatal	0 (0.0)	0 (0.0)
Immediately life threatening	3 (0.7)	0 (0.0)
Disability/incapacity	2 (0.4)	0 (0.0)
Requires hospitalisation	35 (7.7)	39 (8.6)
Prolonged hospitalisation	3 (0.7)	1 (0.2)
Congenital anomaly	0 (0.0)	0 (0.0)
Other	3 (0.7)	0 (0.0)

A patient may be counted in more than one seriousness criterion. Percentages are calculated using total number of patients per treatment as the denominator.

Kerstjens et al. *NEJM* 2012;367:1198-1207.

Adverse events reported by >2% of randomised patients in pooled groups

Primo TinA

	Tiotropium Respimat® n (%)	Placebo Respimat® n (%)
Patients with any AE, n (%)	335 (73.5)	366 (80.3)
Asthma	182 (39.9)	232 (50.9)*
Nasopharyngitis	51 (11.2)	56 (12.3)
Peak expiratory flow rate decreased	93 (20.4)	122 (26.8)
Headache	29 (6.4)	33 (7.2)
Bronchitis	25 (5.5)	20 (4.4)
Sinusitis	16 (3.5)	22 (4.8)
Upper respiratory tract infection	21 (4.6)	16 (3.5)
Influenza	20 (4.4)	14 (3.1)
Cough	13 (2.9)	13 (2.9)
Rhinitis allergic	13 (2.9)*	3 (0.7)
Pneumonia	12 (2.6)	7 (1.5)
Back pain	11 (2.4)	12 (2.6)
Arthralgia	10 (2.2)	9 (2.0)
Dysphonia	10 (2.2)	8 (1.8)
Oropharyngeal pain	9 (2.0)	11 (2.4)
Diarrhoea	8 (1.8)	10 (2.2)
Respiratory tract infection	7 (1.5)	11 (2.4)
Hypertension	6 (1.3)	10 (2.2)
Insomnia	2 (0.4)	10 (2.2)*

Kerstjens et al. *NEJM* 2012;367:1198-1207. Dry mouth reported in 3 (0.7%) placebo Respimat® and 8 (1.8%) tiotropium Respimat® patients; *P<0.05.

Add-on tiotropium independent of phenotypes

Primo TinA/MezzoTin A-subgroup analysis

Tiotropium Decreases The Risk Of Exacerbations In Patients With Symptomatic Asthma Regardless Of Baseline Characteristics

H. A.M. Kerstjens[1], D. P. Tashkin[2], M. Engel[3], R. Dahl[4], P. Paggiaro[5], E. Beck[6], M. Vandewalker[7], W. Seibold[8], P. Moroni-Zentgraf[3], H. Schmidt[3], E. D. Bateman[9],

[1]University Medical Center Groningen, Groningen, Netherlands, [2]David Geffen School of Medicine UCLA, Los Angeles, CA, [3]Boehringer Ingelheim Pharma GmbH & Co KG, Ingelheim am Rhein, Germany, [4]Institute for Clinical Medicine, Aarhus University, Aarhus, Denmark, [5]Pulmonary Unit, University Hospital of Pisa, Pisa, Italy, [6]Institut für Gesundheitsförderung, Rüdersdorf Brandenburg, Germany, [7]Allergy and Asthma Consultants, Jefferson City, MO, [8]Boehringer Ingelheim Pharma GmbH & Co KG, Biberach an der Riss, Germany, [9]Department of Medicine, University of Cape Town, Cape Town, South Africa

- **Basic demographics, BMI, disease characteristics, allergic status, medications including omalizumab and OCS…**

Original Article

Tiotropium Respimat Add-on Is Efficacious in Symptomatic Asthma, Independent of T2 Phenotype

Thomas B. Casale, MD[a], Eric D. Bateman, MD[b], Mark Vandewalker, MD[c], J. Christian Virchow, MD[d], Hendrik Schmidt, PhD[e], Michael Engel, MD[f], Petra Moroni-Zentgraf, MD[g], and Huib A.M. Kerstjens, MD[h] *Tampa, Fla; Cape Town, South Africa; Columbia, Mo; Rostock, Biberach an der Riss, and Ingelheim am Rhein, Germany; Sydney, NSW, Australia; and Groningen, The Netherlands*

End point	Trial pool	Treatment effect, 95% CI, *P* value
Peak FEV_1	PrimoTinA-asthma 5 µg	Mean difference 0.110 (0.063-0.158), $P < .0001$
Peak FEV_1	MezzoTinA-asthma 5 µg	Mean difference 0.185 (0.146-0.223), $P < .0001$
Peak FEV_1	MezzoTinA-asthma 2.5 µg	Mean difference 0.223 (0.185-0.262), $P < .0001$
Trough FEV_1	PrimoTinA-asthma 5 µg	Mean difference 0.093 (0.050-0.137), $P < .0001$
Trough FEV_1	MezzoTinA-asthma 5 µg	Mean difference 0.146 (0.105-0.188), $P < .0001$
Trough FEV_1	MezzoTinA-asthma 2.5 µg	Mean difference 0.180 (0.138-0.221), $P < .0001$
Severe exacerbations	PrimoTinA-asthma 5 µg	HR 0.79 (0.62-1.00), $P = .0343$
Severe exacerbations	MezzoTinA-asthma 5 µg	HR 0.72 (0.45-1.14), $P = .1644$
Severe exacerbations	MezzoTinA-asthma 2.5 µg	HR 0.50 (0.30-0.84), $P = .0084$
Asthma worsening	PrimoTinA-asthma 5 µg	HR 0.69 (0.58-0.82), $P < .0001$
Asthma worsening	MezzoTinA-asthma 5 µg	HR 0.87 (0.69-1.08), $P = .2112$
Asthma worsening	MezzoTinA-asthma 2.5 µg	HR 0.66 (0.52-0.84), $P = .0007$
ACQ-7 responder	PrimoTinA-asthma 5 µg	OR 1.32 (1.01-1.73), $P = .0427$
ACQ-7 responder	MezzoTinA-asthma 5 µg	OR 1.32 (1.02-1.71), $P = .0348$
ACQ-7 responder	MezzoTinA-asthma 2.5 µg	OR 1.33 (1.03-1.72), $P = .0308$

Kerstjens et al. AJRCCM 2013; 187:A4217; J Allergy Clin Immunol Pract 2018;6:923-35

Add-on Tiotropium to ICS or ICS-LABA in asthma

Caden TinA

- **Double blind, randomized, placebo controlled, parallel (52 weeks)**
- **Moderate to severe asthma**
- Tio 5ug (n=114) Tio 2.5ug (n=114) Placebo (n=57)

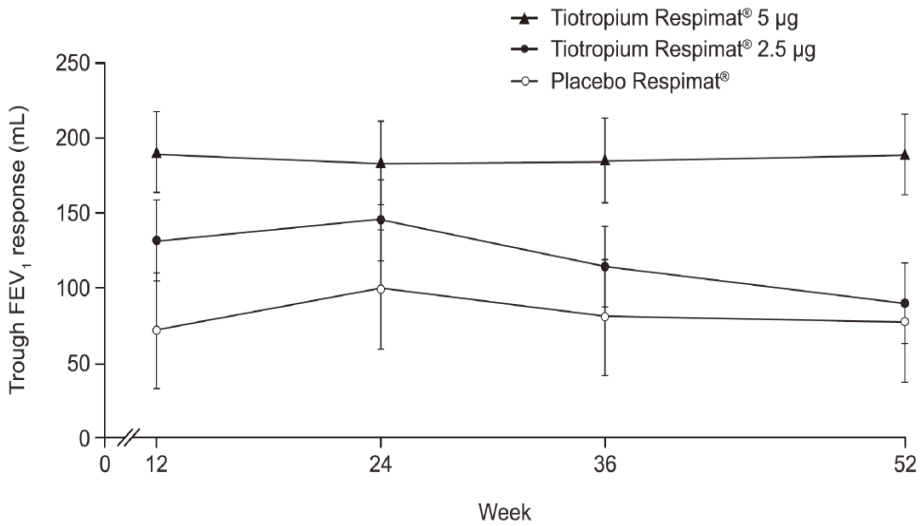
RESEARCH ARTICLE

Long-Term Once-Daily Tiotropium Respimat® Is Well Tolerated and Maintains Efficacy over 52 Weeks in Patients with Symptomatic Asthma in Japan: A Randomised, Placebo-Controlled Study

Ken Ohta[1]*, Masakazu Ichinose[2], Yuji Tohda[3], Michael Engel[4], Petra Moroni-Zentgraf[4], Satoko Kunimitsu[5], Wataru Sakamoto[6], Mitsuru Adachi[7]

Table 2. Overall summary of adverse events (treated set).

n (%)	Tiotropium Respimat 5 µg (n = 114)[a]	Tiotropium Respimat 2.5 µg (n = 114)[a]	Placebo Respimat (n = 57)[a]
Any AE	101 (88.6)	99 (86.8)	51 (89.5)
Severe AEs	2 (1.8)	1 (0.9)	3 (5.3)
Drug-related AEs[b]	10 (8.8)	6 (5.3)	3 (5.3)
AEs leading to discontinuation	2 (1.8)	1 (0.9)	1 (1.8)
Significant (pre-specified) AEs[c]	0	0	0
Serious AEs	4 (3.5)	4 (3.5)	9 (15.8)
Requiring hospitalisation	4 (3.5)	4 (3.5)	7 (12.3)
Drug-related	0	0	1 (1.8)[d]
Fatal	0	0	0
Other	0	0	2 (3.5)



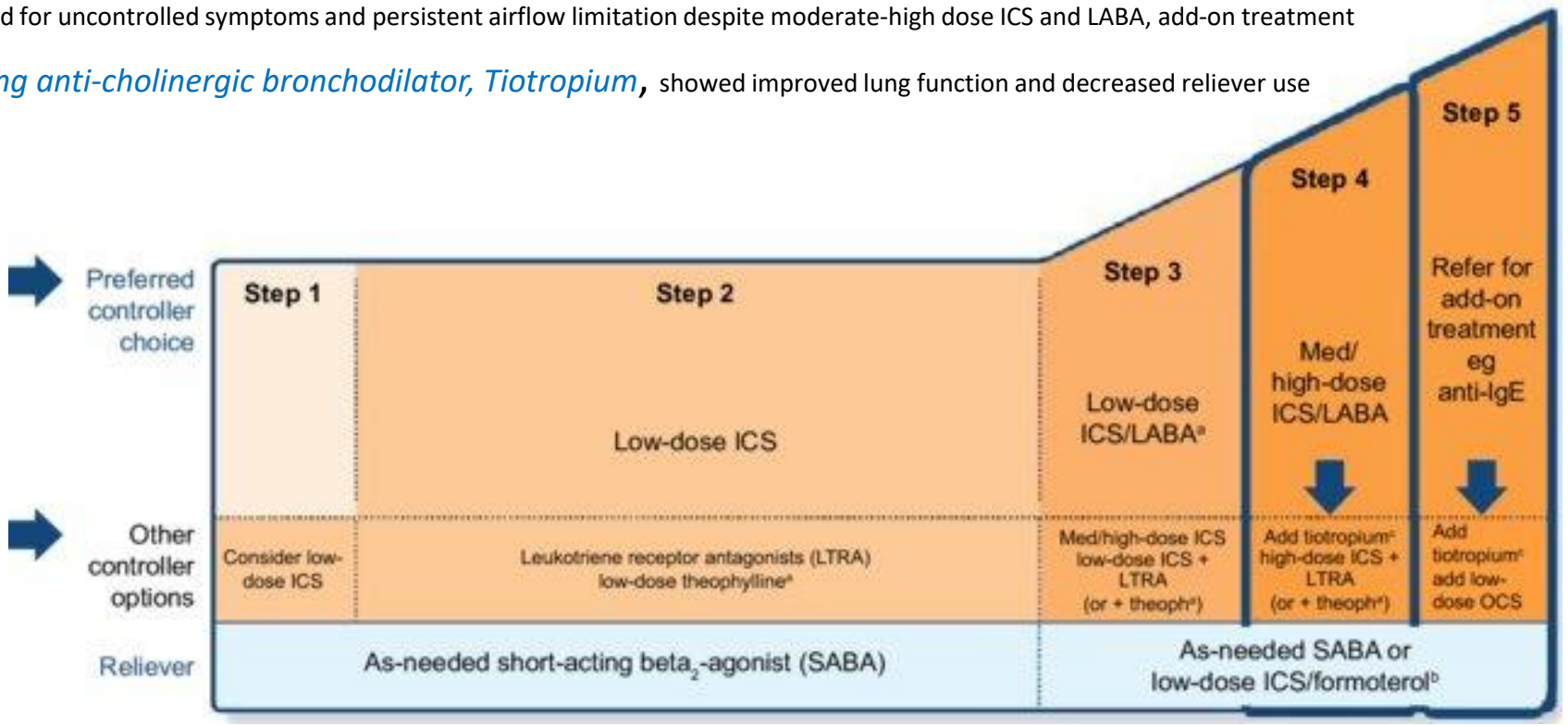
PLoS ONE 10(4): e0124109. Apr 2015

2015 GINA Guideline

Note the recommendation to add tiotropium in steps 4 and 5, after maximizing other medical therapy

- **Add-on treatments without phenotyping**

- … In patients selected for uncontrolled symptoms and persistent airflow limitation despite moderate-high dose ICS and LABA, add-on treatment with the *long acting anti-cholinergic bronchodilator, Tiotropium*, showed improved lung function and decreased reliever use



Global strategy for asthma management and prevention updated 2015

4. Triple therapy in a single inhaler: a new option for uncontrolled asthma

Triple therapy combinations of ICS-LABA-LAMA in a single inhaler (SITT)

Drug Class	Generic Name	Form	Dose
LABA/LAMA/ ICS	Formoterol/tiotropium/ciclesonide	Inhalation powder	12/18/400 μg once-a-day
	Formoterol/glycopyrronium/beclomethasone dipropionate	Inhalation spray	5/11/87 μg twice-a-day
	Vilanterol/umeclidinium/fluticasone furoate	Inhalation powder	22/65/92 μg once-a-day
	Formoterol/glycopyrronium/budesonide	Inhalation aerosol	9.6/14.4/320 μg twice-a-day
	Indacaterol/glycopyrronium/mometasone furoate	Inhalation powder	150/50/80 or 160 μg once-a-day

- Several triple therapy combinations of ICS-LABA-LAMA in a single inhaler (SITT) have been marketed
- 2021 GINA recommends adding a LAMA in patients aged ≥18 years who, despite being adherent to inhaled LABA combined with medium or high doses ICS, still experience symptoms or exacerbations

Allergy. 2021 Sep 3. doi: 10.1111/all.15076. Epub ahead of print; Pharmacol Rev 72:218–252, January 2020

Key SITT studies in patients with asthma

Study	Single-inhaler triple therapy	Comparator(s)	Population	Primary endpoint(s)	Key secondary endpoint(s)
TRIMARAN and TRIGGER (Virchow et al) [47]	BDP/FF/G (TRIMARAN 100/6/10 µg; TRIGGER 200/6/10 µg, both 2 inhalations BID)	TRIMARAN: BDP/FF 100/6 µg, 2 inhalations BID TRIGGER: BDP/FF 200/6 µg, 2 inhalations BID, and BDP/FF 200/6 µg, 2 inhalations BID plus tiotropium 2.5 µg, 2 inhalations OD	Pre-bronchodilator FEV_1 <80% predicted; reversibility >12% and >200 mL; ACQ-7 ≥1.5; ≥1 exacerbation in the previous year; stable dose of ICS/LABA for ≥4 weeks before study entry (TRIMARAN medium ICS dose; TRIGGER high ICS dose)	Morning pre-dose FEV_1 at Week 26 and rate of moderate and severe exacerbations over 52 weeks	Peak FEV_1 at Week 26 and average morning PEF over the first 26 weeks in each study, and the rate of severe exacerbations using data pooled from the two studies.
IRIDIUM (Kerstjens et al) [48]	MF/IND/GLY 80/150/50 and 160/150/50 µg, both 1 inhalation OD	MF/IND 160/150 and 320/150 µg 1 inhalation OD; FLU/SAL 500/50 µg 1 inhalation BID	Pre-bronchodilator FEV_1 <80% predicted; reversibility ≥12% and ≥200 mL; ACQ-7 ≥1.5; ≥1 exacerbation in the previous year; medium/high-dose ICS/LABA for ≥3 months, stable for ≥1 month before study entry	Trough FEV_1 at Week 26	ACQ-7 at Week 26
ARGON (Gessner et al) [49]	MF/IND/GLY 80/150/50 and 160/150/50 µg OD	FLU/SAL 500/50 µg BID + tiotropium 5 µg OD	Pre-bronchodilator FEV_1 <85% predicted; reversibility ≥12% and ≥200 mL; ACQ-7 ≥1.5; ≥1 exacerbation in the previous year; stable medium/high-dose ICS/LABA	AQLQ at Week 24 (non-inferiority)	Not applicable
CAPTAIN (Lee et al) [50]	FluF/UMEC/VI 100/31.25/25, 100/62.5/25, 200/31.25/25, and 200/62.5/25 µg, 1 inhalation OD	FluF/VI 100/25, 200/25 µg, 1 inhalation OD	Pre-bronchodilator FEV_1 30–80% predicted; reversibility ≥12% and ≥200 mL; ACQ-6 ≥1.5; ≥1 healthcare contact or change in therapy for acute asthma symptoms in the previous year; medium/high-dose ICS/LABA for ≥12 weeks, stable for ≥6 weeks	Trough FEV_1 at Week 24	Annualised rate of moderate and/or severe exacerbations

BDP, beclometasone dipropionate; FF, formoterol fumarate; G, glycopyrronium; BID, twice daily; OD, once daily; FEV_1, forced expiratory volume in 1 second; ACQ, Asthma Control Questionnaire; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; PEF, peak expiratory flow; MF, mometasone furoate; IND, indacaterol acetate; GLY, glycopyrronium bromide; FLU, fluticasone; SAL, salmeterol; AQLQ, Asthma Quality of Life Questionnaire; FluF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol.

Key SITT studies in patients with asthma, ongoing

KALOS (NCT04609878) study

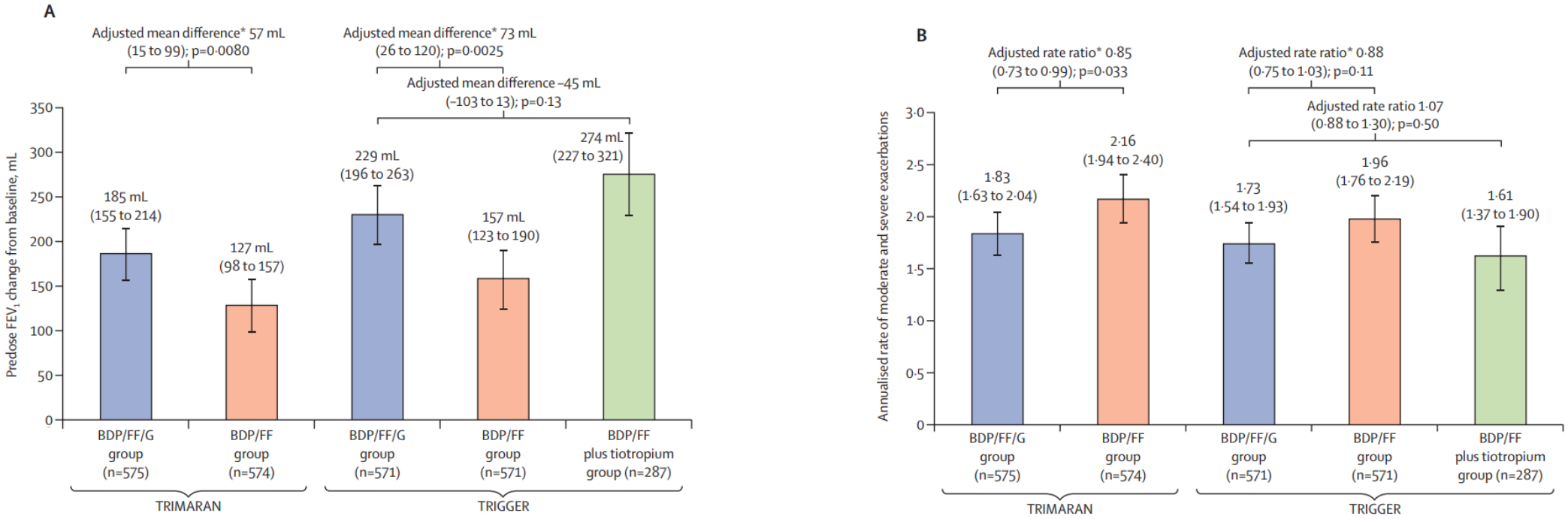
Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	2800 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Primary Purpose:	Treatment
Official Title:	A Randomized, Double-Blind, Double Dummy, Parallel Group, Multicenter Variable Length Study to Assess the Efficacy and Safety of PT010 Relative to PT009 and Symbicort® in Adult and Adolescent Participants With Inadequately Controlled Asthma
Actual Study Start Date :	December 15, 2020
Estimated Primary Completion Date :	July 25, 2023
Estimated Study Completion Date :	July 25, 2023

SITT in asthma
TRIMARAN and TRIGGER

Single inhaler extrafine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): two double-blind, parallel-group, randomised, controlled phase 3 trials

Johann Christian Virchow, Piotr Kuna, Pierluigi Paggiaro, Alberto Papi, Dave Singh, Sandrine Corre, Florence Zuccaro, Andrea Vele, Maxim Kots, George Georges, Stefano Petruzzelli, Giorgio Walter Canonica**

- Two parallel-group, double-blind, randomised, active-controlled, phase 3 trials (26 weeks, 52 weeks)
- Uncontrolled asthma (TRIMARAN, n=1155, TRIGGER, n=1437)
- TRIMARAN (BDP/FF/G vs BDP/FF); TRIGGER (BDP/FF/G vs BDP/FF vs BDP/FF +TIO)

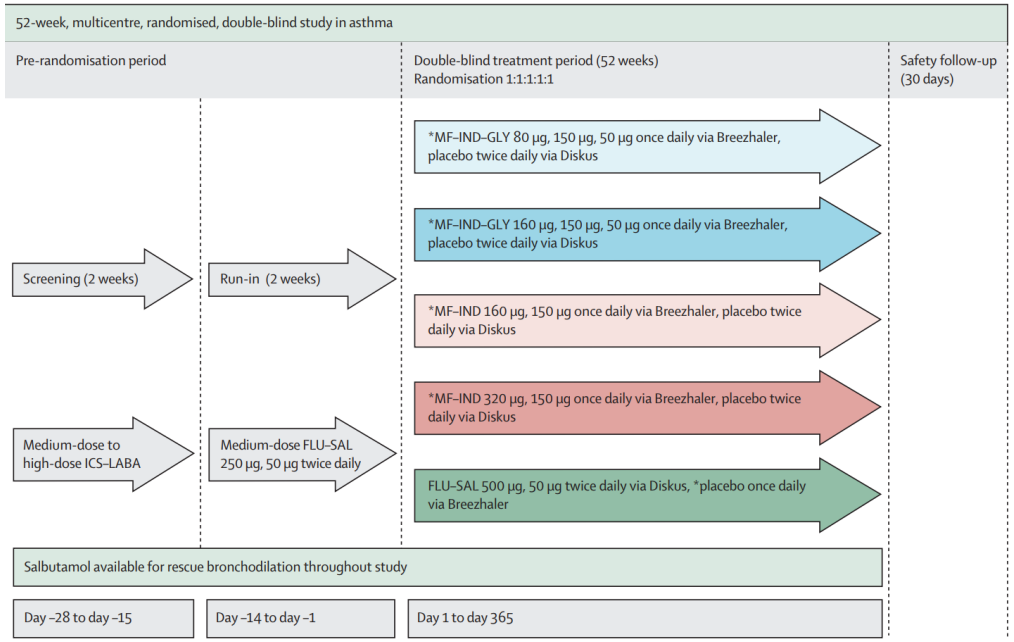


Lancet 2019; 394: 1737–49

Triple therapy had a greater effect on (a) change in pre-dose FEV1 from baseline to Week 26 (57 mL in TRIMARAN, p=0.0080; 73 mL in TRIGGER, p=0.0025) and (b) the rate of moderate and severe exacerbations (15% lower in TRIMARAN, p=0.033; 12% lower in TRIGGER, p=0.11).

SITT in asthma
IRIDIUM

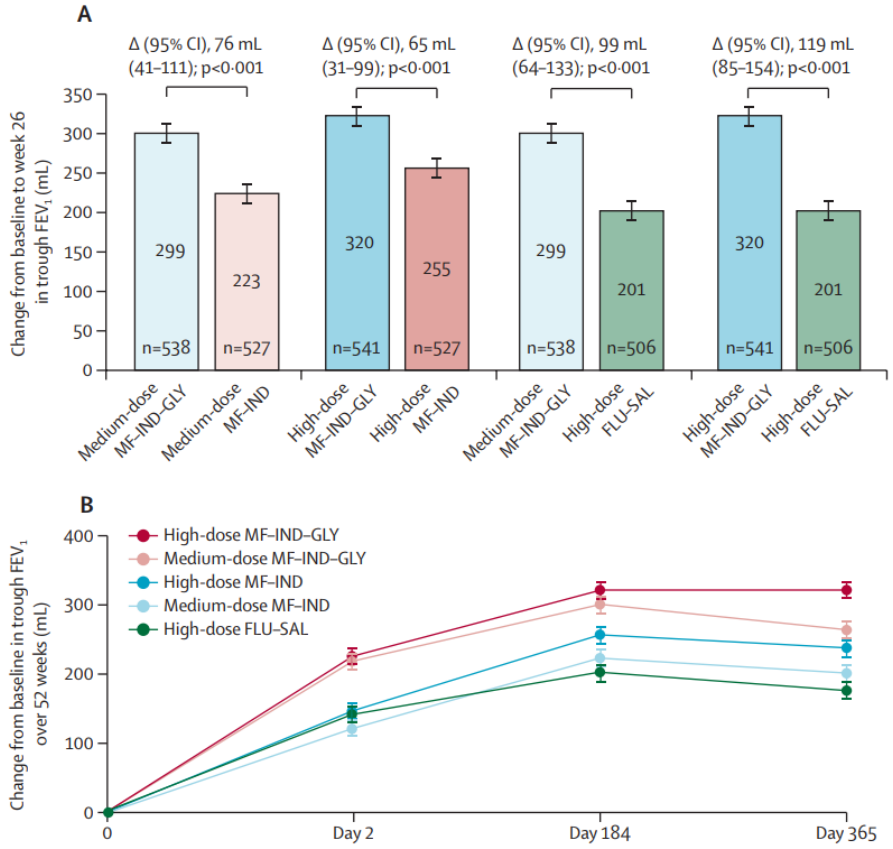
- **Double-blind, double-dummy, parallel-group, active-controlled phase 3 study (52 weeks)**
- **Uncontrolled asthma**
- Medium dose MF/IND/GLY (n=620), High dose MF/IND/GLY (n=619), Medium dose MF/IND (n=617), High dose MF/IND (n=618), High dose FLU/SAL(n=618)



Once-daily, single-inhaler MF–IND–GLY improved lung function versus ICS–LABA combinations (MF–IND and FLU–SAL) in patients with inadequately controlled asthma.

Once-daily, single-inhaler mometasone–indacaterol–glycopyrronium versus mometasone–indacaterol or twice-daily fluticasone–salmeterol in patients with inadequately controlled asthma (IRIDIUM): a randomised, double-blind, controlled phase 3 study

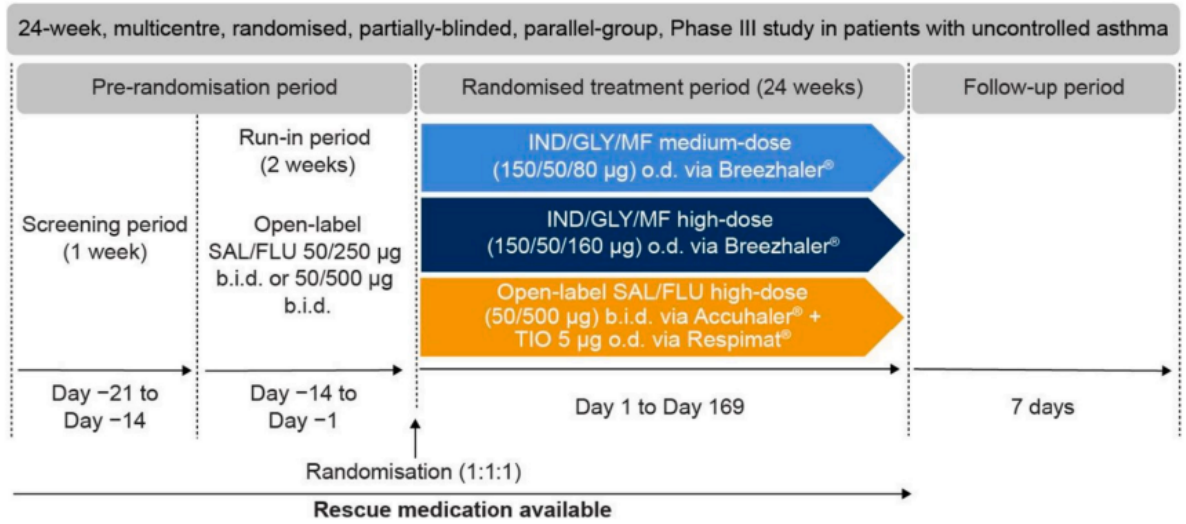
*Huib A M Kerstjens, Jorge Maspero, Kenneth R Chapman, Richard N van Zyl-Smit, Motoi Hosoe, Ana-Maria Tanase, Catherine Lavecchia, Abhijit Pethe, Xu Shu, Peter D'Andrea, on behalf of the IRIDIUM trial investigators**



Lancet Respir Med 2020;8: 1000–12

SITT in asthma
ARGON

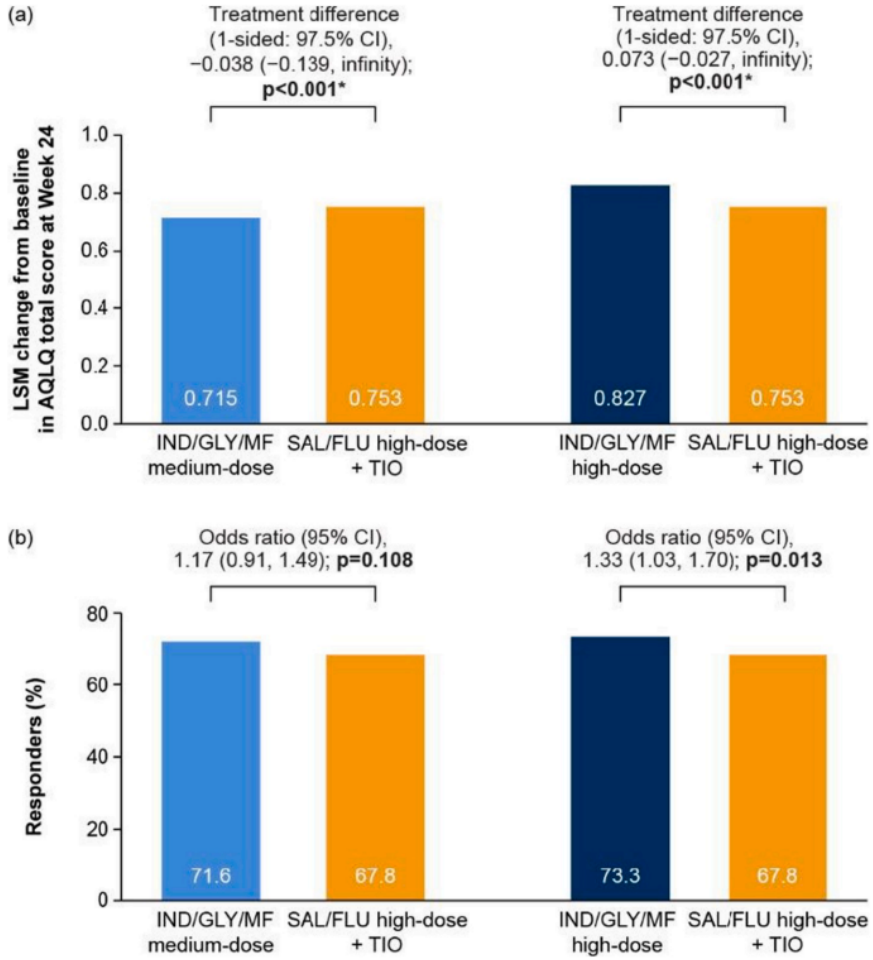
- **Partially-blinded, randomised, 24-week, parallel-group, non-inferiority, open-label, active-controlled Phase IIIb study (24 weeks)**
- **Uncontrolled asthma**
- Medium dose MF/IND/GLY (n=474), High dose MF/IND/GLY (n=476), High dose FLU/SAL+ TIO (n=476)



IND/GLY/MF high- and medium-dose o.d. via a single inhaler were non-inferior to SAL/FLU highdose b.i.d. þ TIO o.d. via two inhalers for AQLQ.

Fixed-dose combination of indacaterol/glycopyrronium/mometasone furoate once-daily *versus* salmeterol/fluticasone twice-daily plus tiotropium once-daily in patients with uncontrolled asthma: A randomised, Phase IIIb, non-inferiority study (ARGON)

Christian Gessner [a,*], Oliver Kornmann [b], Jorge Maspero [c], Richard van Zyl-Smit [d], Matthias Krüll [e], Anna Salina [f], Pritam Gupta [g], Sebastien Bostel [f], Sebastian Fucile [h], Lorena Garcia Conde [f], Pascal Pfister [f]



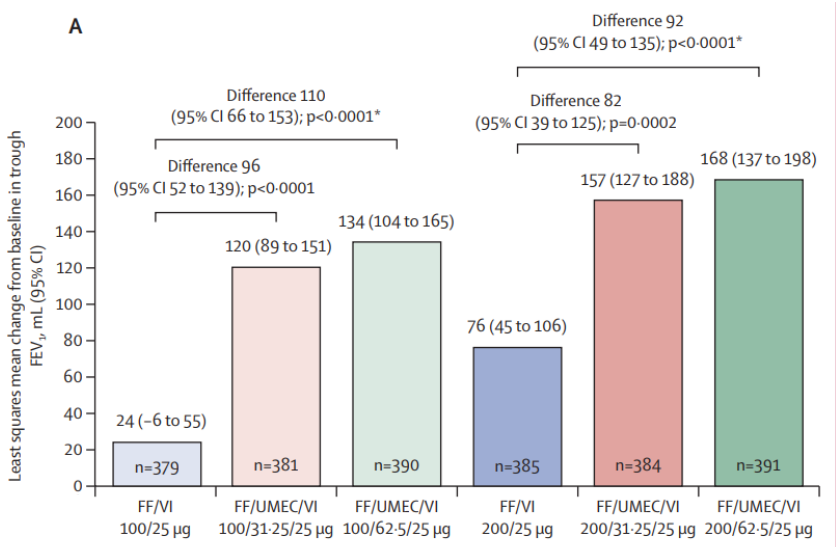
Respiratory Medicine 170 (2020) 106021

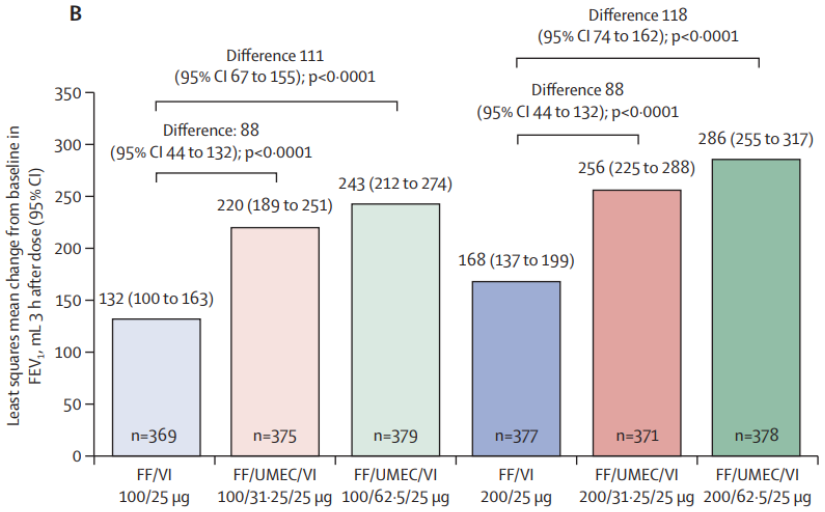
SITT in asthma
CAPTAIN

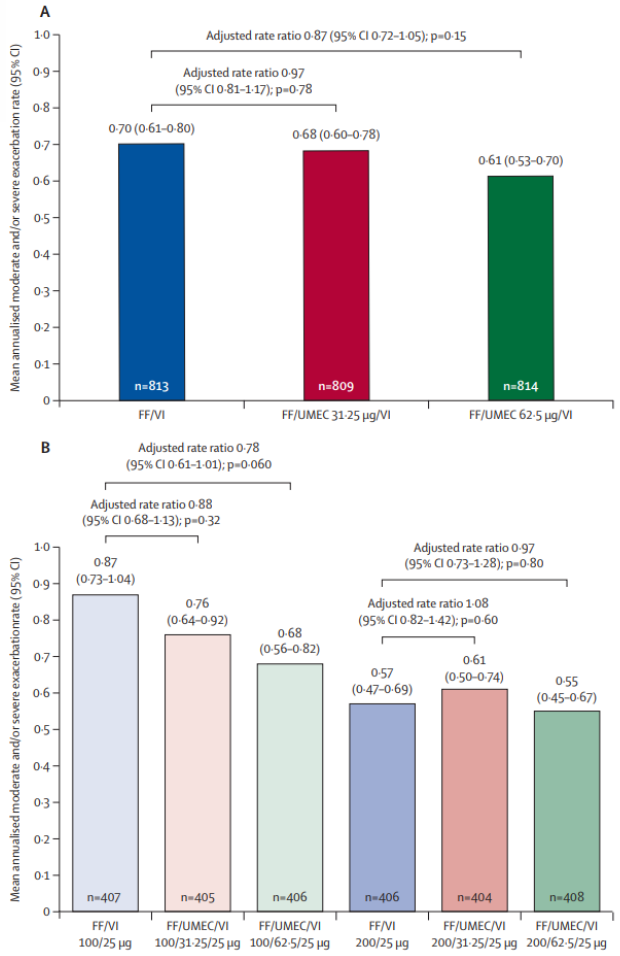
Efficacy and safety of once-daily single-inhaler triple therapy (FF/UMEC/VI) versus FF/VI in patients with inadequately controlled asthma (CAPTAIN): a double-blind, randomised, phase 3A trial

Laurie A Lee, Zelie Bailes, Neil Barnes, Louis-Philippe Boulet, Dawn Edwards, Andrew Fowler, Nicola A Hanania, Huib A M Kerstjens, Edward Kerwin, Robert Nathan, John Oppenheimer, Alberto Papi, Steven Pascoe, Guy Brusselle, Guy Peachey, Neal Sule, Maggie Tabberer, Ian D Pavord

- **Double-blind, randomised, parallel-group, phase 3A study (52 weeks)**
- **Uncontrolled asthma**
- FF/VI (100/25 µg n=407; 200/25 µg n=406) or FF/UMEC/VI (100/31·25/25 µg n=405; 100/62·5/25 µg n=406; 200/31·25/25 µg n=404; 200/62·5/25 µg n=408)





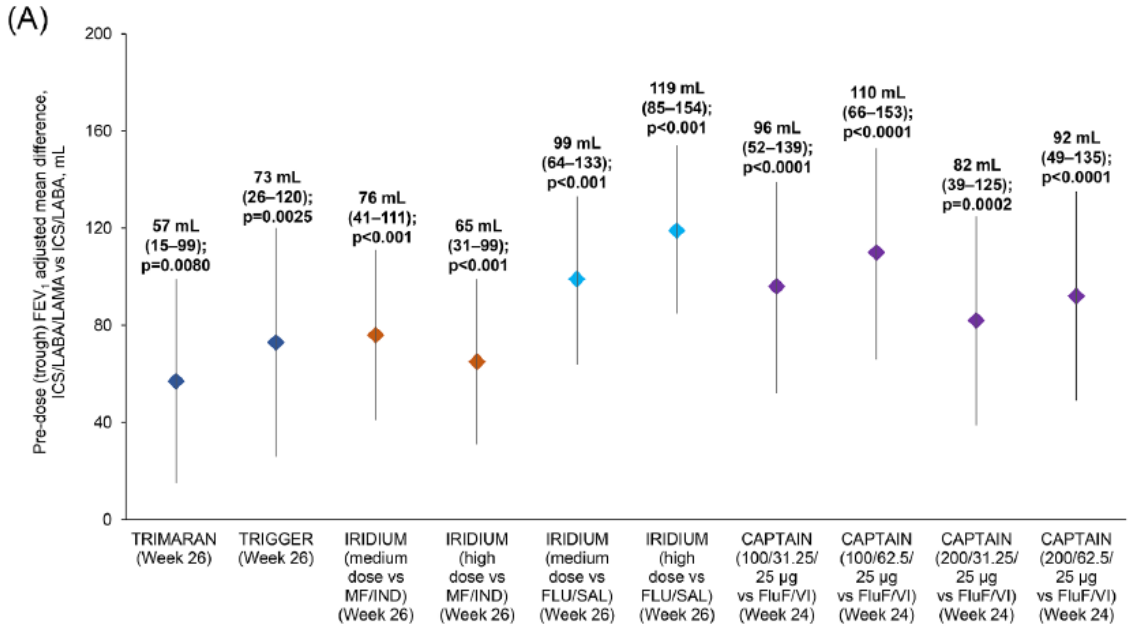


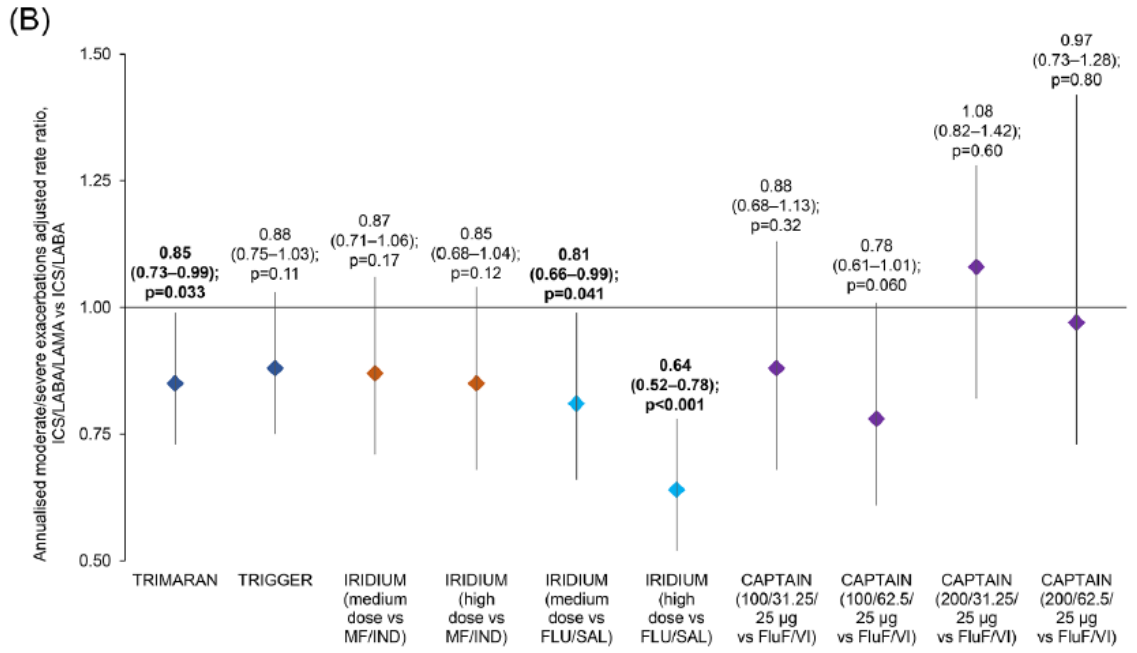
In patients with uncontrolled moderate or severe asthma on ICS/LABA, adding UMEC improved lung function but did not lead to a significant reduction in moderate and/or severe exacerbations.

Lancet Respir Med 2021;9: 69–84

Key SITT studies in patients with asthma

SITT Compared to ICS/LABA





FEV1 difference

Exacerbation rate ratio

European Journal of Internal Medicine 85 (2021) 14–22

5. LAMA in mild to moderate asthma

Steroids in Eosinophil Negative Asthma (SIENA) trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mometasone or Tiotropium in Mild Asthma with a Low Sputum Eosinophil Level

S.C. Lazarus, J.A. Krishnan, T.S. King, J.E. Lang, K.V. Blake, R. Covar, N. Lugogo, S. Wenzel, V.M. Chinchilli, D.T. Mauger, A.-M. Dyer, H.A. Boushey, J.V. Fahy, P.G. Woodruff, L.B. Bacharier, M.D. Cabana, J.C. Cardet, M. Castro, J. Chmiel, L. Denlinger, E. DiMango, A.M. Fitzpatrick, D. Gentile, A. Hastie, F. Holguin, E. Israel, D. Jackson, M. Kraft, C. LaForce, R.F. Lemanske, Jr., F.D. Martinez, W. Moore, W.J. Morgan, J.N. Moy, R. Myers, S.P. Peters, W. Phipatanakul, J.A. Pongracic, L. Que, K. Ross, L. Smith, S.J. Szefler, M.E. Wechsler, and C.A. Sorkness, for the National Heart, Lung, and Blood Institute AsthmaNet*

ABSTRACT

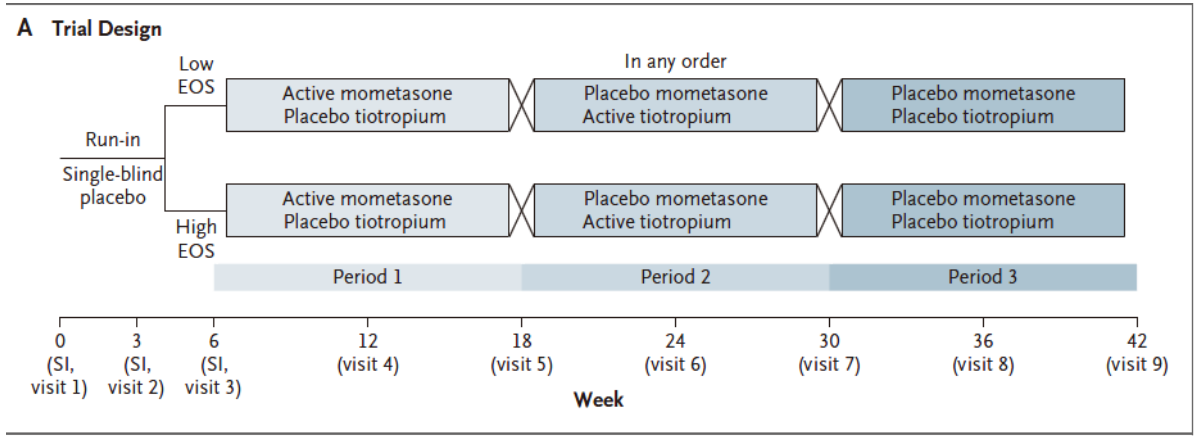
BACKGROUND

In many patients with mild, persistent asthma, the percentage of eosinophils in sputum is less than 2% (low eosinophil level). The appropriate treatment for these patients is unknown.

Patient

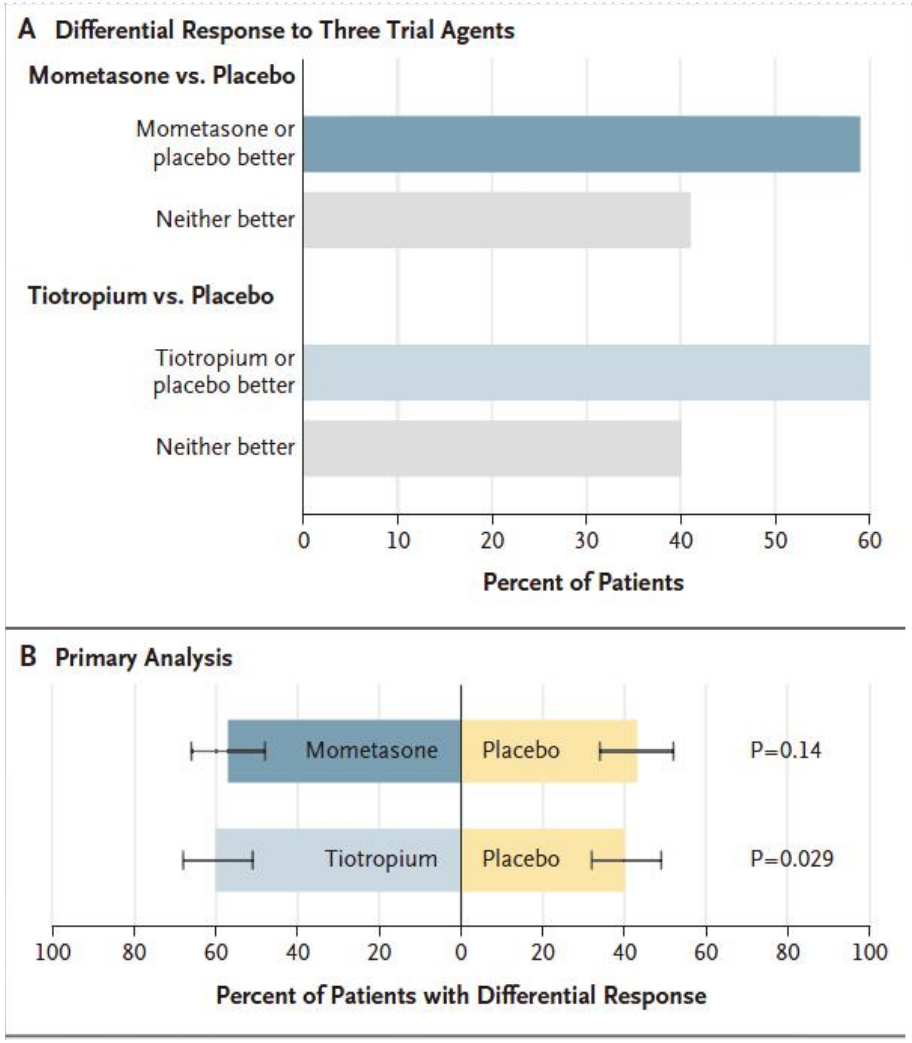
Needed STEP 2 treatment (NHLBI EPR-3)

Sputum EOS 2%



N Engl J Med 2019;380:2009-19.

SIENA trial- Controlled status

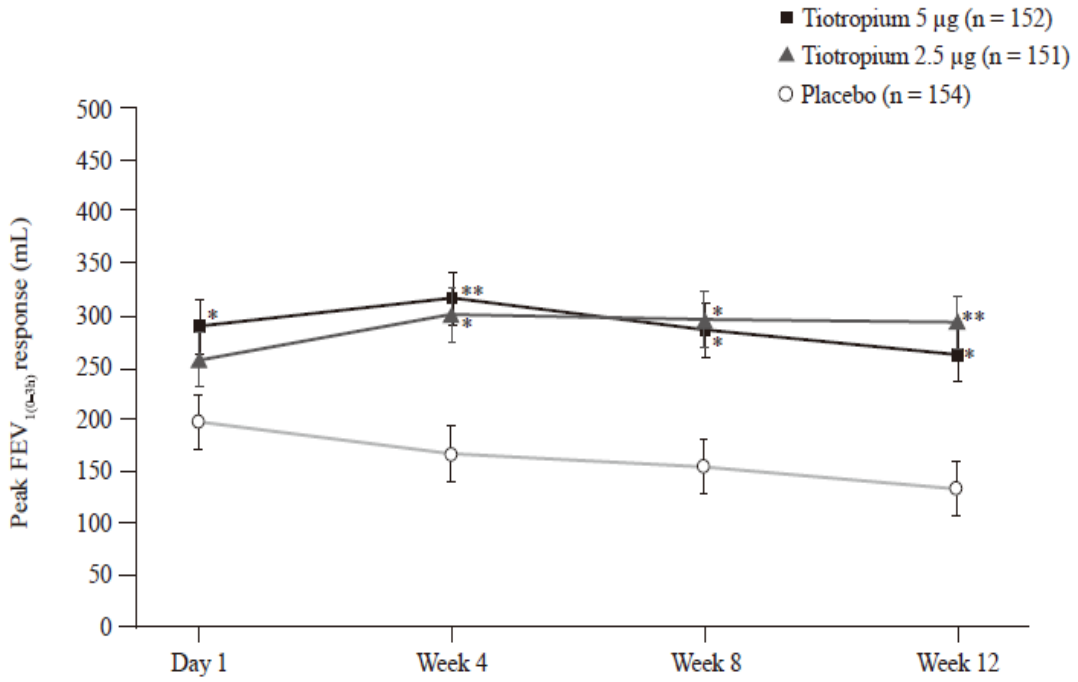


- **The majority of the mild persistent asthma patients, 268 (73%) were classified as having a low eosinophil level and the minor, 98 (27%) as having a high eosinophil level.**
- **They had no significant difference in their response to either mometasone or tiotropium as compared with placebo.**
- **in a secondary analysis in the high-eosinophil stratum, the response to mometasone was clearly superior to the response to placebo.**
- **Clinical equipoise for a larger and longer study to compare inhaled glucocorticoids with other treatments for the large number of patients with mild or moderate asthma.**

N Engl J Med 2019;380:2009-19.

Grazia Tin A-asthma trial

- **A phase III, double-blind, placebo-controlled, parallel-group trial (12 weeks)**
- **Mild to moderate persistent asthma**
- TIO 5 µg (n=155), TIO 2.5 µg (n=154), or placebo (n=155) add-on to low- to medium dose ICS

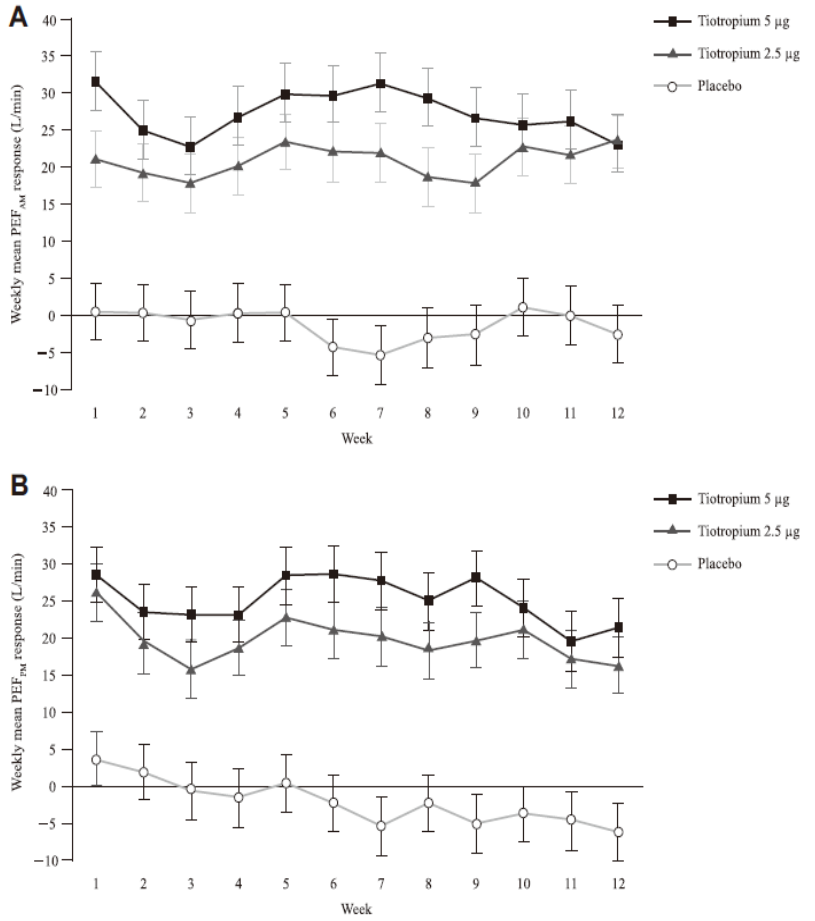


Once-daily tiotropium Respimat add-on therapy to low- to medium-dose ICS in adults with symptomatic asthma is an efficacious bronchodilator, and its safety and tolerability are comparable with those of placebo Respimat.

Original Article

The Effect of Tiotropium in Symptomatic Asthma Despite Low- to Medium-Dose Inhaled Corticosteroids: A Randomized Controlled Trial

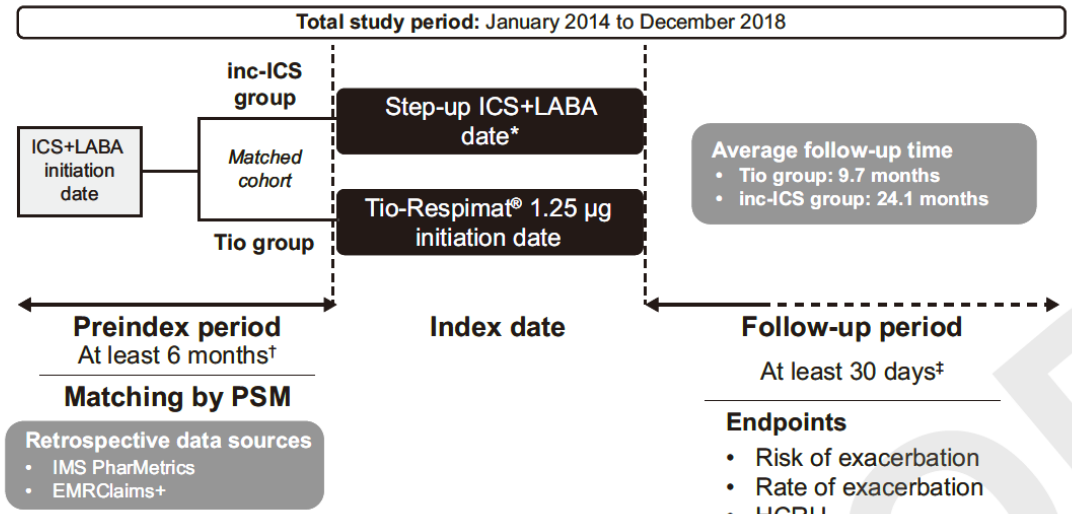
Pierluigi Paggiaro, MD[a], David M.G. Halpin, FRCP[b], Roland Buhl, MD, PhD[c], Michael Engel, MD[d], Valentina B. Zubek, PhD[e], Zuzana Blahova, PharmDr[f], Petra Moroni-Zentgraf, MD[d], and Emilio Pizzichini, DD, PhD[g] *Pisa, Italy; Exeter, UK; Mainz, Ingelheim am Rhein, Germany; Ridgefield, Conn; Vienna, Austria; and Florianópolis, Brazil*

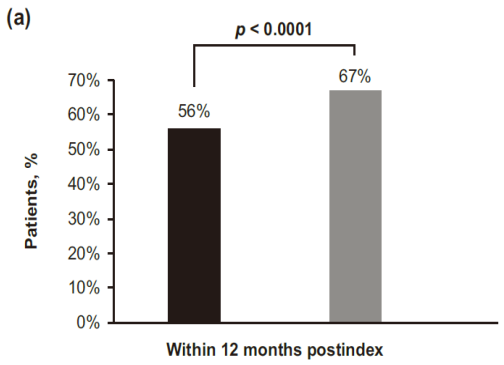


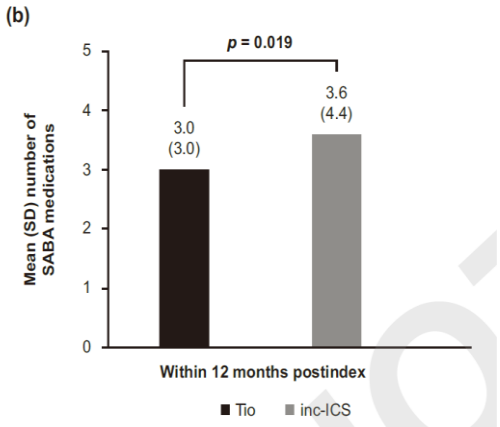
J Allergy Clin Immunol Pract 2016;4:104-13

6. Perspectives

Early application of triple therapy in asthma?

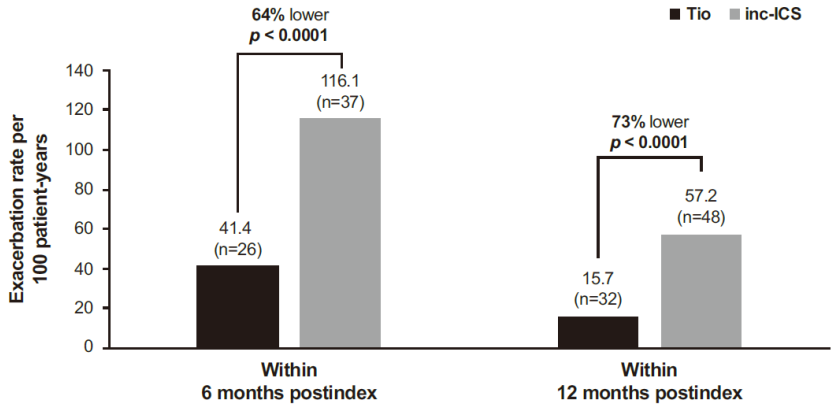


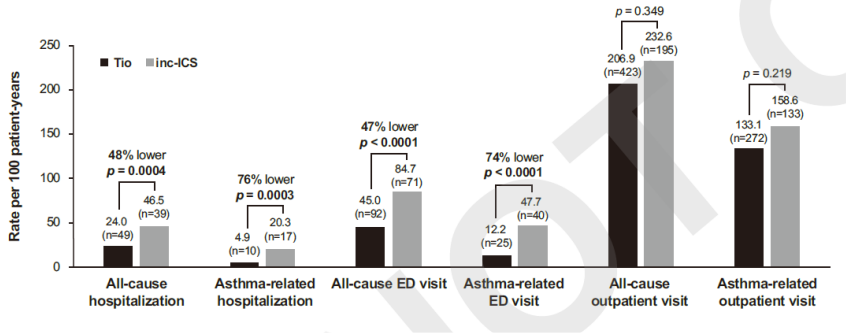




Add-on tiotropium versus step-up inhaled corticosteroid plus long-acting beta-2–agonist in real-world patients with asthma

Bradley Chipps, M.D.,[1] Giselle Mosnaim, M.D.,[2] Sameer K. Mathur, M.D.,[3] Asif Shaikh, M.D.,[4] Samir Khoury, M.D.,[4] Gokul Gopalan, M.D.,[4] Swetha R. Palli, M.S.,[4] Lois Lamerato, Ph.D.,[5] Julian Casciano, B.S.,[6] Zenobia Dotiwala, M.S.,[6] and Russell Settipane, M.D.[7]





Allergy Asthma Proc 41:248–255, 2020

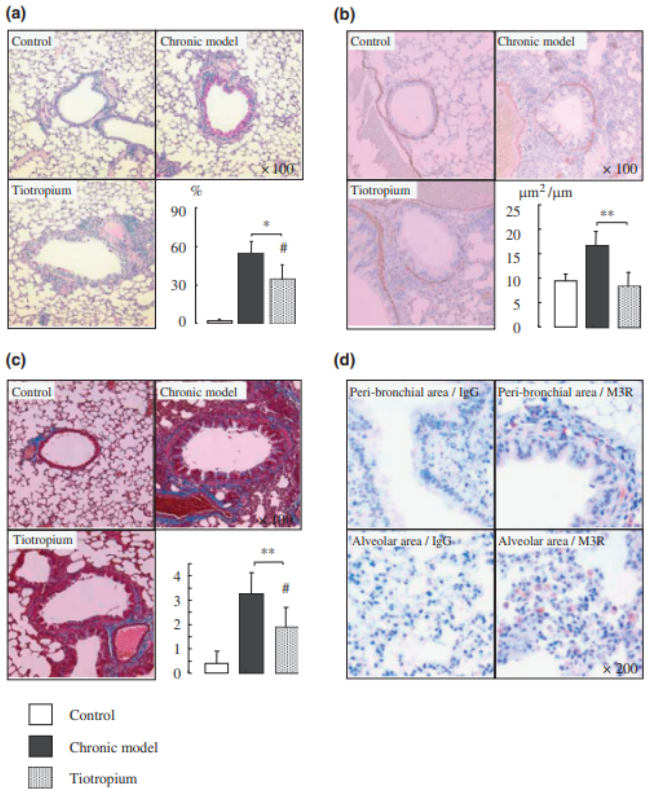
Positioning LAMA in personalized therapy in asthma

Airway remodeling: pre-clinical level

Effect of tiotropium bromide on airway inflammation and remodelling in a mouse model of asthma

S. Ohta[1], N. Oda[1], T. Yokoe[1], A. Tanaka[1], Y. Yamamoto[1], Y. Watanabe[1], K. Minoguchi[2], T. Ohnishi[1], T. Hirose[1], H. Nagase[3], K. Ohta[3] and M. Adachi[1]

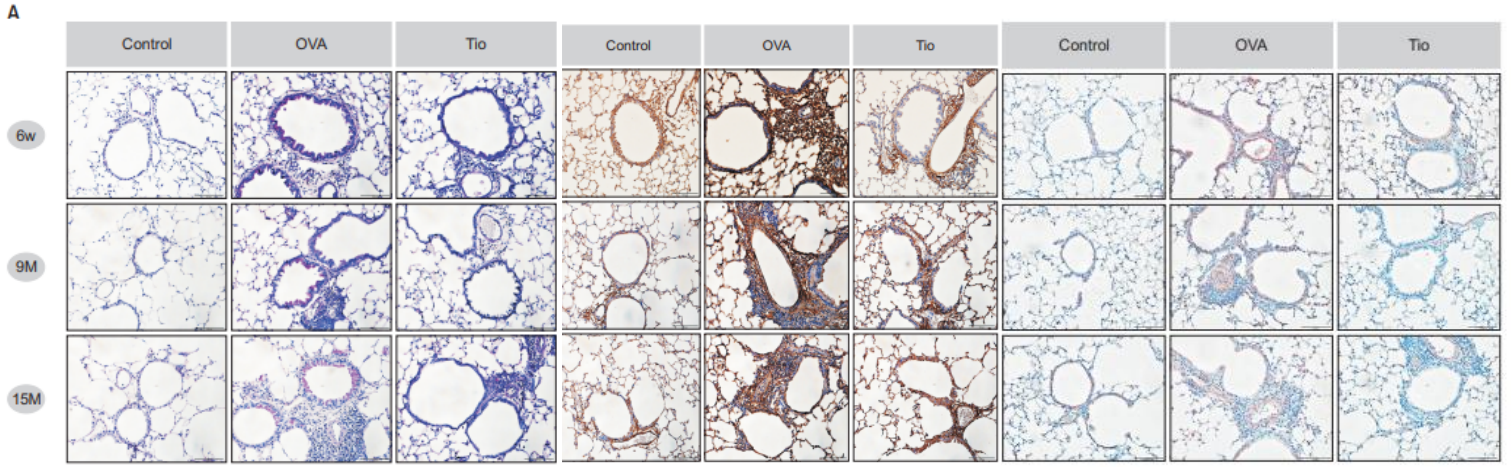
[1]Department of Internal Medicine, Division of Allergy and Respiratory Medicine, School of Medicine, Showa University, Tokyo, Japan, [2]Sumiregaoka Clinic, Kanagawa, Japan and [3]Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan



ORIGINAL ARTICLE | https://doi.org/10.4046/trd.2018.0049
ISSN: 1738-3536(Print)/2005-6184(Online) • Tuberc Respir Dis 2019;82:71-80

Expression of Muscarinic Receptors and the Effect of Tiotropium Bromide in Aged Mouse Model of Chronic Asthma

Ji Young Kang, M.D., Ph.D., In Kyoung Kim, Ph.D., Jung Hur, Ph.D., Seok Chan Kim, M.D., Ph.D., Sook Young Lee, M.D., Ph.D., Soon Seog Kwon, M.D., Ph.D. and Young Kyoon Kim, M.D., Ph.D.
Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea



Tuberc Respir Dis 2019;82:71-80; Clinical & Experimental Allergy, 2010;40, 1266–1275

Positioning LAMA in personalized therapy in asthma

LAMA monotherapy or ICS-LAMA in a specific phenotype?

- LAMA should never be used as monotherapy in asthmatic patients and, anyway, there is scarce evidence showing that ICS/LABA can be replaced by ICS/LAMA.

- Considering
  - Low eosinophilic mild asthma
  - Smokers
  - ACO patients

Positioning LAMA in personalized therapy in asthma

vs. Biologics

- LAMA is cost-effective and substantially less expensive than biological therapies.
- It seems that LAMA is ideally placed as an add-on therapy that can be trialled in patients prior to additional phenotype-guided therapies or increased ICS dose.
- LAMA is much less effective in terms of the reduction of exacerbations and no data are available to show a systemic steroid-sparing effect, specifically in T2 phenotypes.
- LAMA has no biomarkers to manage the patients with asthma.

Summary and conclusion

- The use of LAMAs in asthma is supported from a mechanistic perspective, with evidence from a series of experimental and clinical studies.
- Drug interaction of LAMA with ICS and LABA shows synergistic effects, supporting combination therapy including SITT.
- Current guidelines recommends adding a LAMA in patients with asthma, despite being adherent to ICS-LABA, still experience symptoms or exacerbations.
- Data from SITT clinical studies in asthma support to expect the better asthma control and the improvement of adherence in patients.
- Further investigation is needed for several unanswered questions regarding the LAMA use in asthma, in particular personalized treatment.


Thank you for your attention….