Insights and Controversies from the Asthma Guidelines

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BRIGHAM HEALTH

BWH BRIGHAM AND WOMEN'S The Lung Center

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SEVERE ASTHMA PROGRAM

Conflicts of Interest

None.

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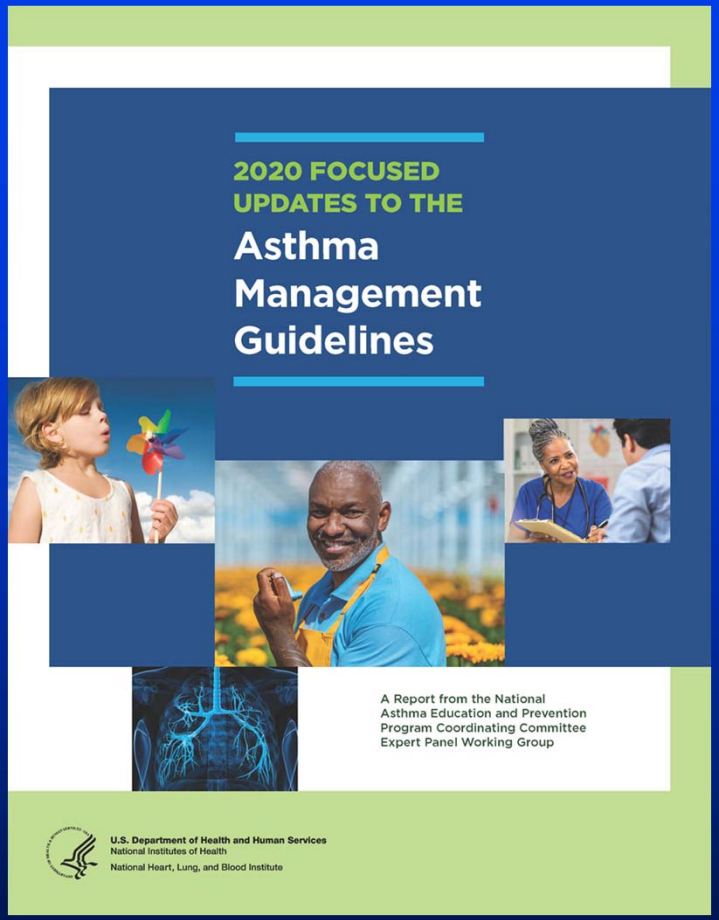

nhlbi.nih.gov/health-topics/asthma-management-guidelines-2020-updates

ginasthma.org/gina-reports

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Case Example

A 27-year-old woman, mother of two, with long-standing asthma is currently treated with fluticasone/salmeterol 250/50 one inhalation twice daily and montelukast 10 mg daily.

She presents with night-time awakenings at least once a week due to her asthma; and in the last year has had two courses of prednisone for asthma flares triggered by respiratory tract infections.

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Case Example (cont.)

She has cough with clear sputum production and friends have commented on her wheezing.

Spirometry reveals mild airflow obstruction with an FEV_1 = 72% of predicted.

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Case Example

Is this:

Difficult-to-Control Asthma

or

Severe Asthma?

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Distinguishing Difficult-to-Control vs. Severe Asthma

- A systematic evaluation protocol was applied to 73 sequentially referred patients with poorly controlled asthma (Regional Respiratory Center, Belfast).
- 34/73 (47%) failed to improve and were deemed to have true “therapy resistant asthma.”

Heaney LG, *Thorax* 2003: 58; 561-6.

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Systematic Approach

I. Inciting agents

II. Aggravating conditions

III. Medication non-compliance

IV. Alternative diagnoses

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What "Step-Up" Therapy Would You Choose Next?

- Switch to SMART therapy
- Increase dose of inhaled steroid
- Add long-acting muscarinic antagonist (LAMA) bronchodilator
- Other: lipoxygenase inhibitor (zileuton)

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Stepping Up Therapy – NAEPP 2020

- **Switch to SMART therapy**
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Switching to SMART Therapy

In individuals ages 12 years and older, the preferred Step 4 therapy is single-inhaler ICS-formoterol used both daily and as needed. The recommended alternate therapy of maintenance ICS-LABA along with SABA as quick-relief therapy does not need to be changed if it is providing adequate control. However, individuals whose asthma is uncontrolled on such therapy should receive the preferred SMART if possible before stepping up their treatment to a higher step of therapy.

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ICS-Formoterol

- Budesonide-formoterol MDI (*Symbicort*)
  - 160/4.5 and 80/4.5 mcg
- Mometasone-formoterol MDI (*Dulera*)
  - 50/5, 100/5, and 200/5 mcg

The maximum total daily dose of formoterol should not exceed 12 puffs (54 mcg) for ages 12 and older.

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Literature Review: SMART vs. ICS/LABA plus SABA as needed

- **Kuna P, et al., *Int J Clin Pract* 2007; 61:725-36.**
  - 3,335 subjects; 6-month, double-blind, double-dummy trial; BUD/FOR 160/4.5 BID and prn vs FLU/SAL 250/50 BID and TERB prn (vs. BUD 320/9 BID and TERB prn).
- **Bousquet J, et al. *Respir Med* 2007; 101:2437-46.**
  - 2,309 subjects; 6-month double-blind, double-dummy trial; BUD/FOR 320/9 BID and prn vs FLU/SAL 500/50 BID and TERB prn.
- **Vogelmeier C, et al. *Eur Respir J* 2005; 26:819–28.**
  - 2,143 subjects; 12-month open-label trial; BUD/FOR 320/9 BID and prn vs FLU/SAL 250/50 BID and ALB prn

SMART vs. FLU/SAL + SABA: Outcomes

- Fewer exacerbations, fewer ED visits and hospitalizations favoring SMART therapy.
- No differences in lung function, asthma control, or quality of life (symptom diaries; ACQ-5 and AQLQ scores).
- No differences in self-reported frequency of rescue medication use.

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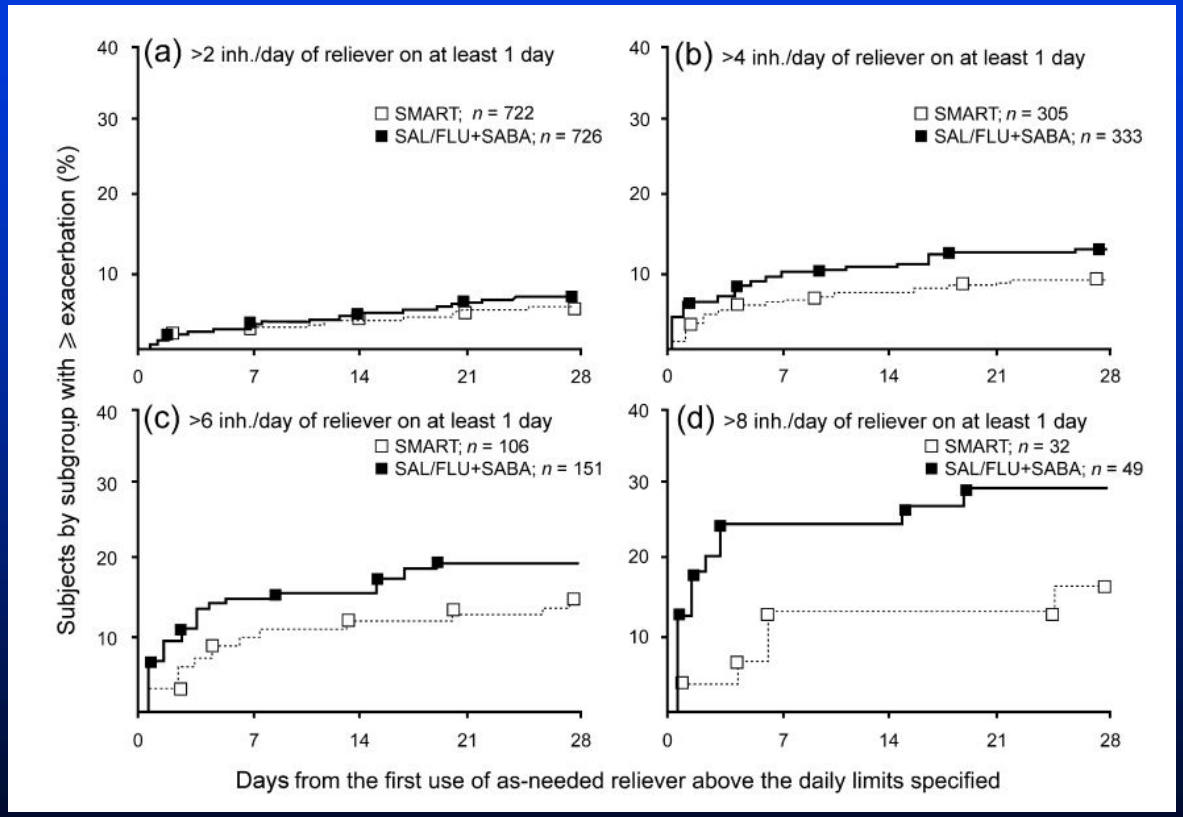
SMART vs. FLU/SAL + SABA: Exacerbations



Bousquet J, et al. *Respir Med* 2007; 101:2437-46.

Patient-Activated, Reliever-Triggered ICS

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Reliever-Triggered Inhaled Glucocorticoid in Black and Latinx Adults with Asthma

E. Israel, J.-C. Cardet, J.K. Carroll, A.L. Fuhlbrigge, L. She, F.W. Rockhold, N.E. Maher, M. Fagan, V.E. Forth, B.P. Yawn, P. Arias Hernandez, J.M. Kruse, B.K. Manning, J. Rodriguez-Louis, J.B. Shields, B. Ericson, A.D. Colon-Moya, S. Madison, T. Coyne-Beasley, G.M. Hammer, B.M. Kaplan, C.S. Rand, J. Robles, O. Thompson, M.E. Wechsler, J.P. Wisnivesky, M.D. McKee, S.P. Jariwala, E. Jerschow, P.J. Busse, D.C. Kaelber, S. Nazario, M.L. Hernandez, A.J. Apter, K.-L. Chang, V. Pinto-Plata, P.M. Stranges, L.P. Hurley, J. Trevor, T.B. Casale, G. Chupp, I.L. Riley, K. Shenoy, M. Pasarica, R.A. Calderon-Candelario, H. Tapp, A. Baydur, and W.D. Pace

Israel E, et al. *N Engl J Med* 2022; 386:1505-18.

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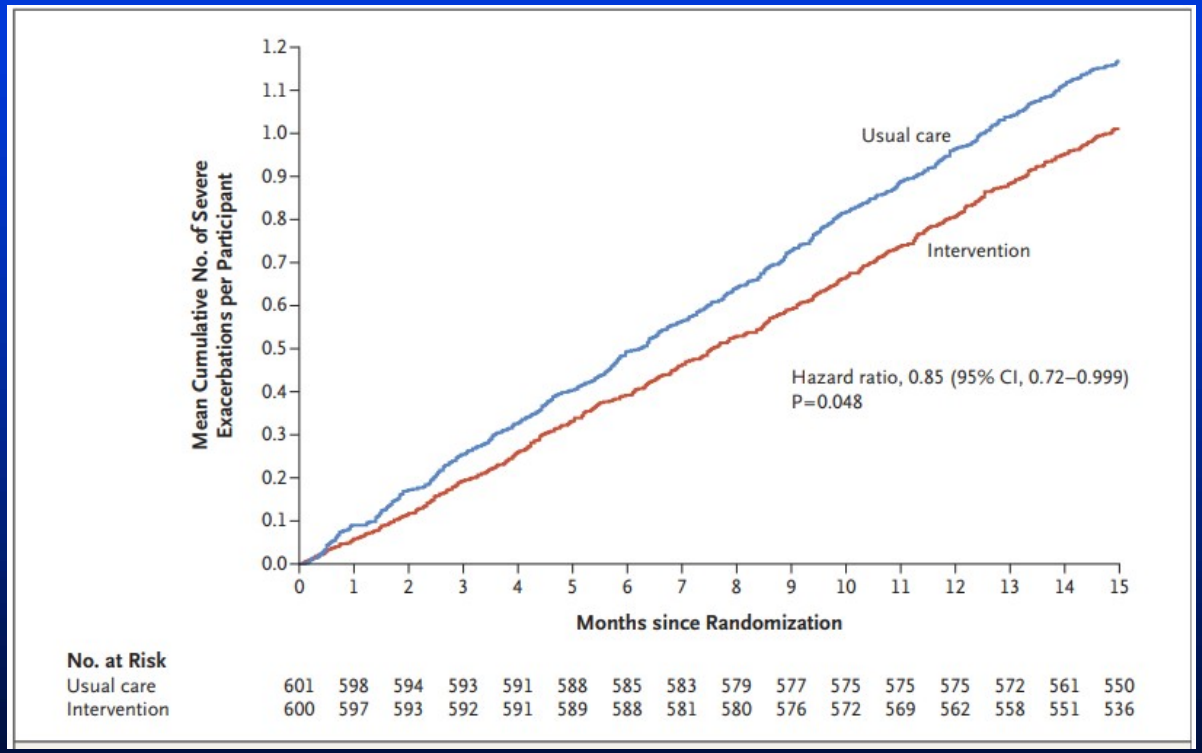
Patient-Activated, Reliever-Triggered ICS



Also,

- Improved asthma control scores.
- Fewer days missed from work/planned activities.

Israel E, et al. *N Engl J Med* 2022; 386:1505-18.

Anti-Inflammatory Rescue ("AIR")

Enter:

Combination budesonide/albuterol (80/90 mcg) MDI (*Air Supra*)

approved by FDA January 2023 for persons aged 18 and older.

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Stepping Up Therapy – NAEPP 2020

- Switch to SMART therapy
- **Increase dose of inhaled steroid**
- Add long-acting muscarinic antagonist (LAMA) bronchodilator
- Other: lipoxygenase inhibitor (zileuton)

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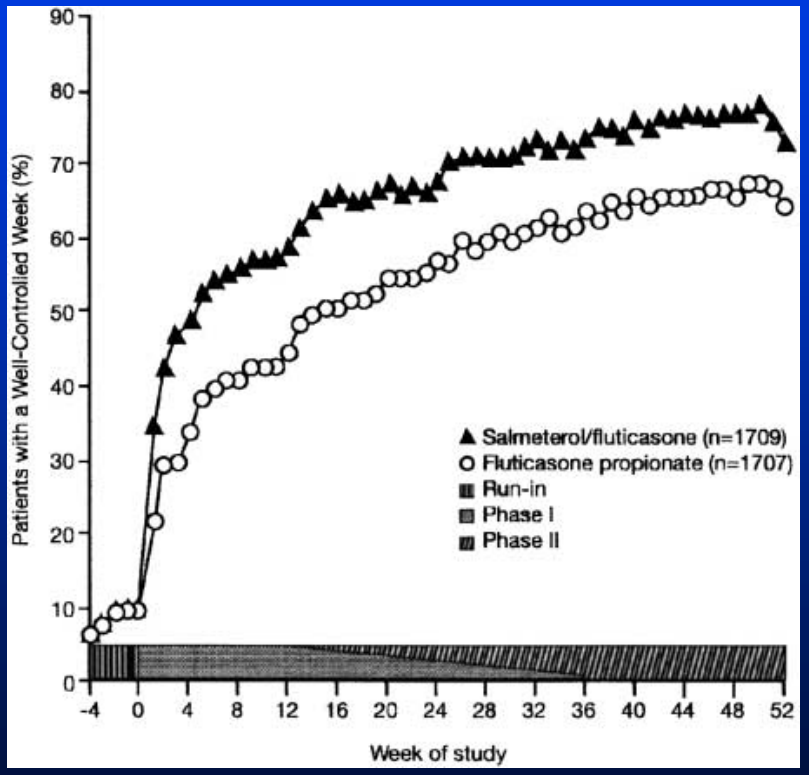
Gaining Optimal Asthma ControL (GOAL)



Bateman BD, et al. *AJRCCM* 2004; 170:836-44.

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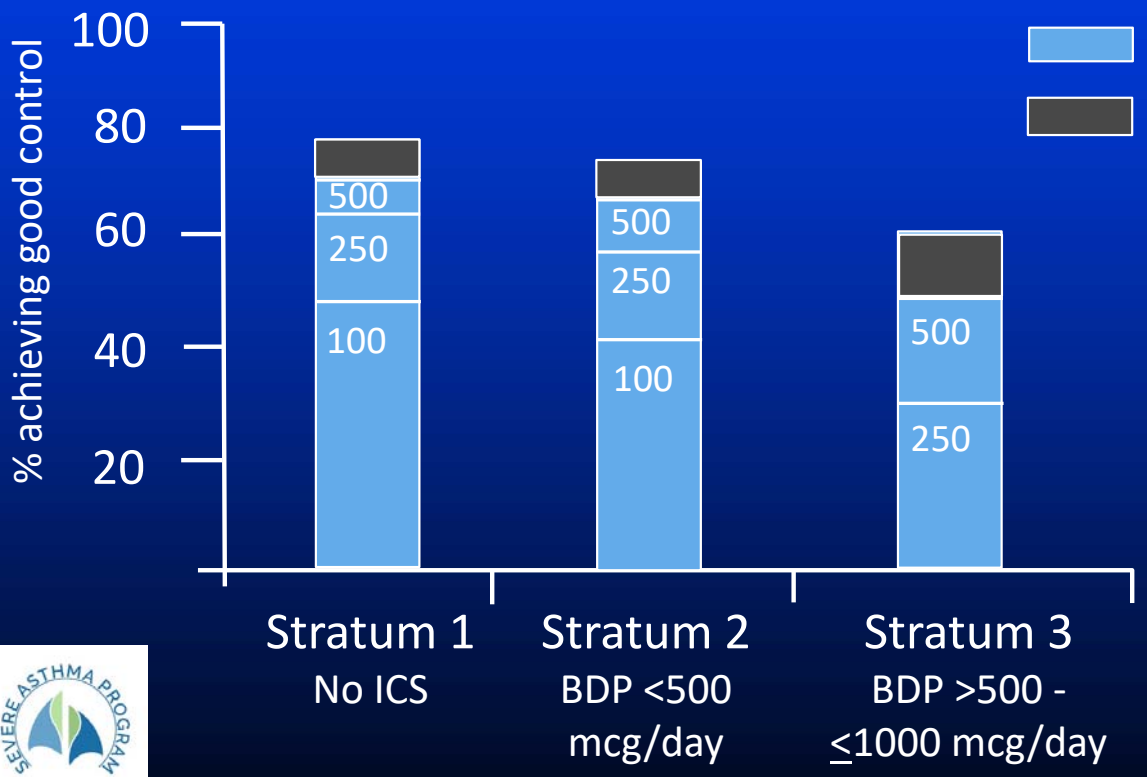
Achieving Control with High-Dose ICS/LABA: (GOAL Study)



Stepping up to FLU/SAL 500/50

Bateman ED, et al., *AJRCCM* 2004; 170:836-44.

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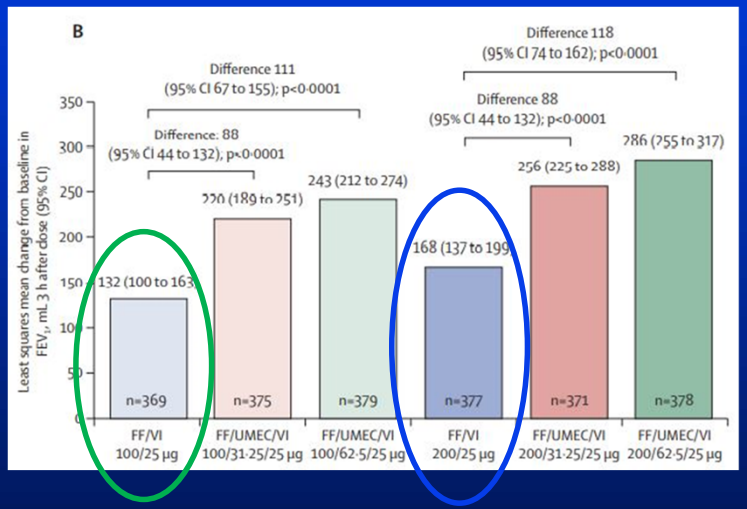
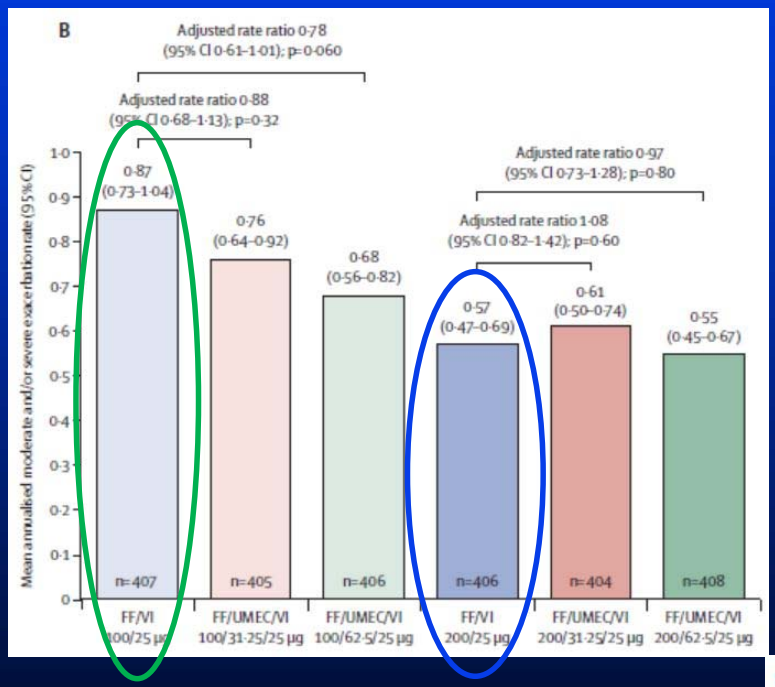
Achieving Control with High-Dose ICS/LABA: (CAPTAIN Study)



Lung function



Exacerbations

Stepping up to fluticasone furoate 200

Lower-dose ICS/LABA

Higher-dose ICS/LABA

Lee LA, et al., *Lancet Respir Med* 2021; 9: 69–84.

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Systemic Effects of Ultra High-Dose ICS (Up to 2000 mcg of fluticasone/day)

Estimated systemic absorption of ultra high-dose ICS from effect on adrenal suppression (lit. review).

	OCS dose reduction in relation to 1000 µg increase in ICS dose (95% CI)	OCS dose resulting in same adrenal suppression as 1000 µg of ICS	Ratio (95% CI)
Fluticasone propionate	4.9 mg (2.4–7.4)	5 mg	1.02 (0.68–2.08)
Budesonide	2.1 mg (1.1–3.2)	2 mg	0.93 (0.63–1.89)

Maijers I, et al., *Eur Respir J* 2020; 55: 1901147.

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- Other: lipoxygenase inhibitor (zileuton)

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Long-Acting Muscarinic Antagonist (LAMA) Added to ICS/LABA

In individuals ages 12 years and older with uncontrolled persistent asthma, the Expert Panel conditionally recommends adding LAMA to ICS-LABA compared to continuing the same dose of ICS-LABA.*

"Conditional recommendation, moderate certainty of evidence"

* LAMA therapy should not be used in individuals with glaucoma or urinary retention.

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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.

- Compared to placebo, tiotropium improved lung function (trial 1 = 86 ml, trial 2 = 154 ml).
- Increased the time to first severe exacerbation (282 vs 226 days), with 21% decrease in risk of severe exacerbation.

Kerstjens HAM, et al. *NEJM* 2012; 367:1198-207.

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- No differences in ACQ-7 or AQLQ.
- No differences in number of symptom-free days.
- No differences in rescue medication use.

Kerstjens HAM, et al. *NEJM* 2012; 367:1198-207.

LAMAs for the Treatment of Asthma

- Dose of tiotropium in *NEJM* study (and GINA recommended) = 5 mcg/day.
- FDA approved dose for asthma = 2.5 mcg/day.
- Also approved for use in asthma = umeclidinium (and likely soon approved: glycopyrrolate)

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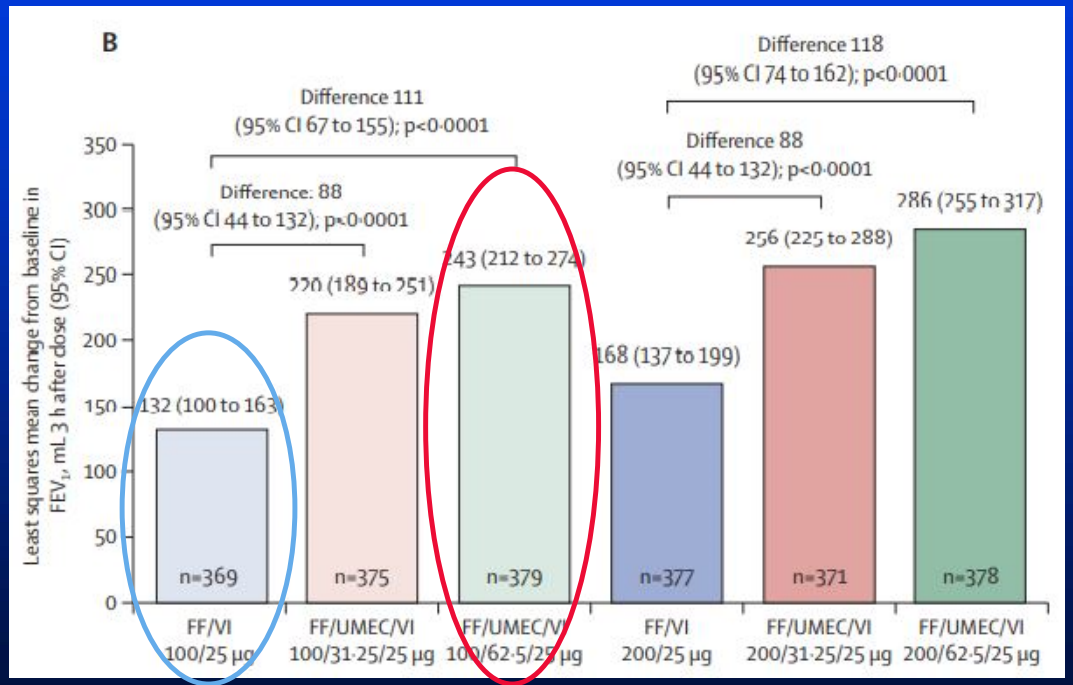
Triple Controller Therapy in Single Device: (CAPTAIN Study)

ICS/LABA

ICS/LABA + LAMA



Lung function

Lee LA, et al., *Lancet Respir Med* 2021; 9: 69–84.

Adding umeclidinium 62.5 mcg to lower-dose ICS

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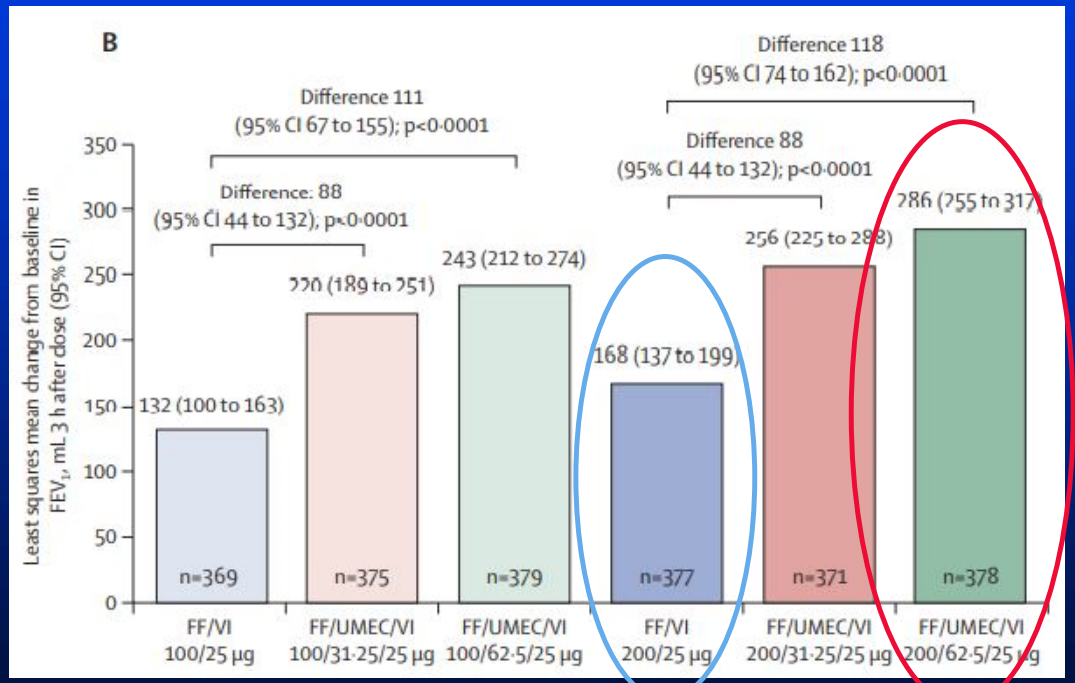
Triple Controller Therapy in Single Device: (CAPTAIN Study)

ICS/LABA

ICS/LABA + LAMA



Lung function

Adding umeclidinium 62.5 mcg to higher-dose ICS

Lee LA, et al., *Lancet Respir Med* 2021; 9: 69–84.

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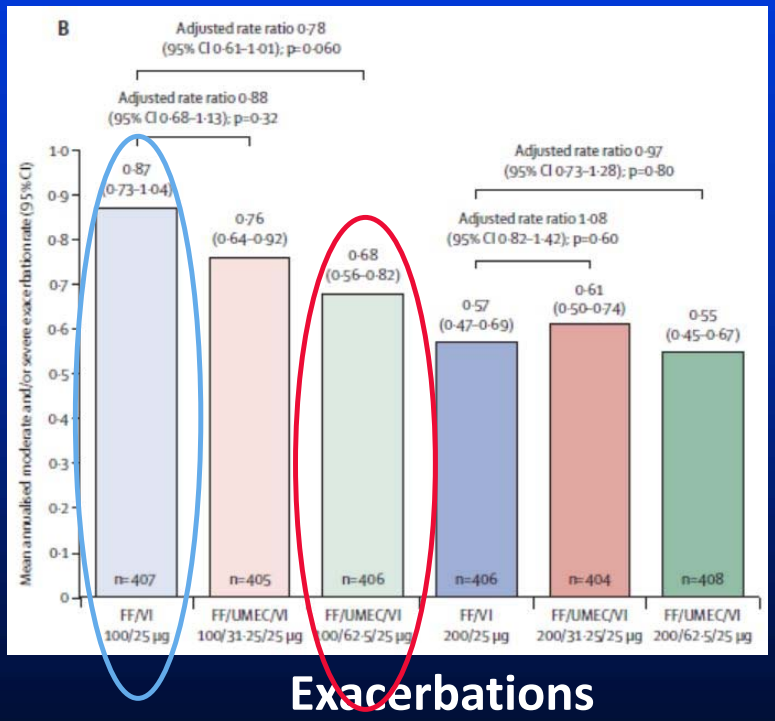
Triple Controller Therapy in Single Device: (CAPTAIN Study)

ICS/LABA

ICS/LABA
+
LAMA



Exacerbations

Adding umeclidinium 62.5 mcg to lower-dose ICS

Lee LA, et al., *Lancet Respir Med* 2021; 9: 69–84.

Combination LABA, LAMA, and ICS

Combination	Brand name	Dose / Delivery System
Vilanterol + umeclidinium + fluticasone furoate* *Once-daily dosing	*Trelegy*	25/62.5/100 25/62.5/200 Multi-dose dry-powder inhaler (*Ellipta*)
Formoterol + glycopyrrolate + budesonide* *Approved for COPD only	*Breztri*	4.8/9/160 Metered-dose inhaler (*Aerosphere*) twice daily

Stepping Up Therapy – NAEPP 2020

- Switch to SMART therapy
- Increase dose of inhaled steroid
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- **Other: lipoxygenase inhibitor (zileuton)**

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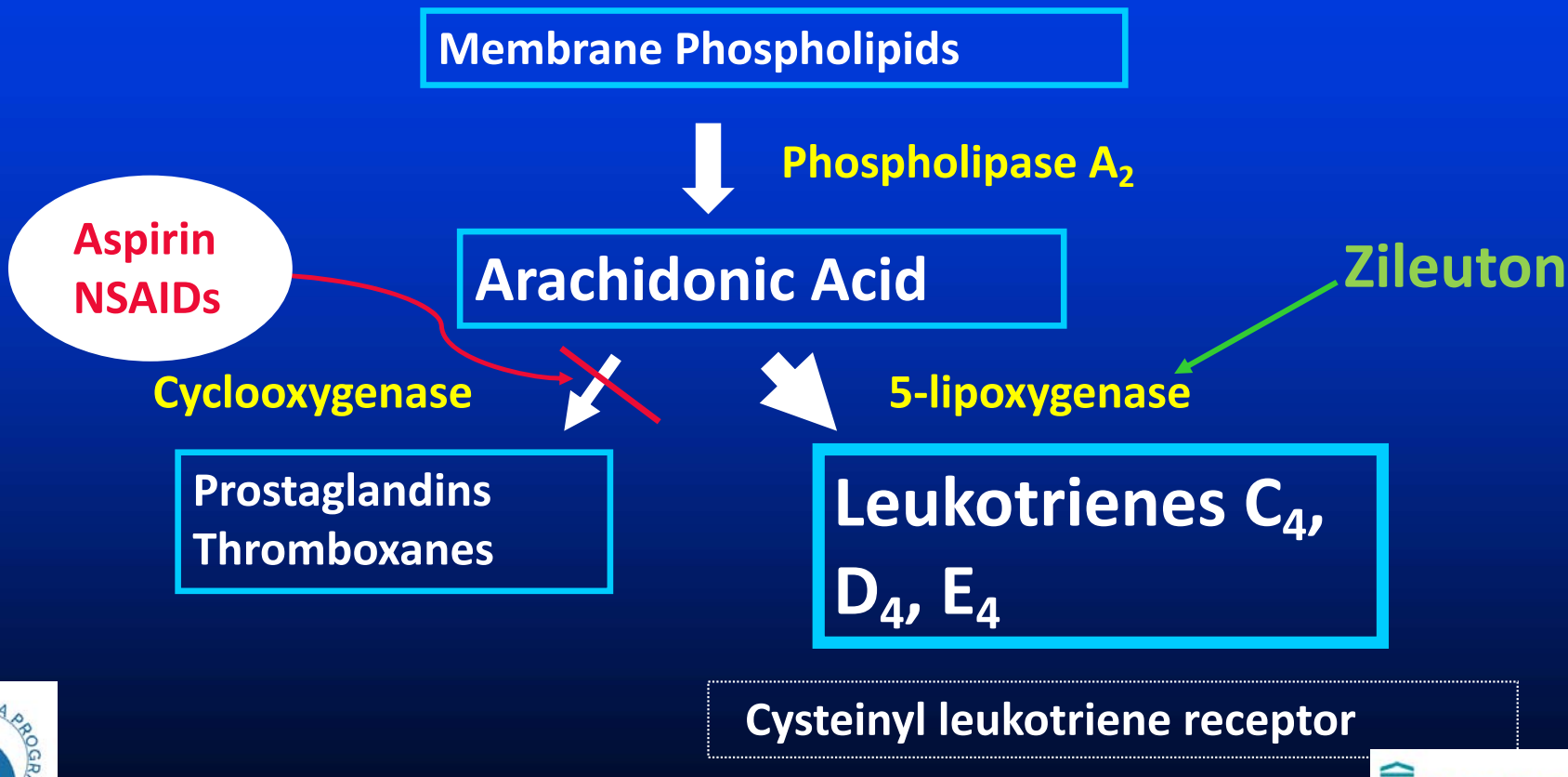
Arachidonic Acid Pathway



Other Options: Azithromycin (Off-Label Recommendation of GINA Guidelines)

- 420 persons with poorly-controlled asthma despite ICS and LABA.
- Randomly assigned to azithromycin 500 mg 3 times/week vs. placebo for 48 weeks.
- Primary outcomes: exacerbations and asthma quality of life.
- Exclusions: impaired hearing; prolong QT interval

Gibson PG, et al. *Lancet* 2017; 390:659-68. ("Asthma and Macrolides: The Azithromycin Efficacy and Safety" [AMAZES] trial)

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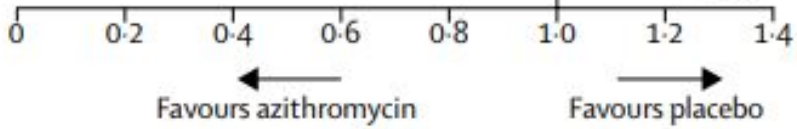
AMAZES Trial: Exacerbations

	Number	Exacerbations per person-year		Incidence rate ratio (95% CI)
		Placebo	Azithromycin	
Non-eosinophilic asthma	224	1·74	1·15	0·66 (0·47–0·93)
Eosinophilic asthma	196	1·98	0·96	0·52 (0·29–0·94)
Inhaled corticosteroid dose adjustment	420	1·86	1·07	0·58 (0·46–0·74)
Frequent exacerbators	140	2·79	1·47	0·55 (0·41–0·73)
Cough and sputum VAS	48	1·72	0·79	0·49 (0·26–0·95)
Bacteria–negative	188	1·85	1·18	0·61 (0·52–0·72)*
Bacteria–positive	48	2·64	1·11	0·39 (0·22–0·69)*



Gibson PG, et al. *Lancet* 2017; 390:659-68.

AMAZES Trial: Other Outcomes

- Improved quality of life (AQLQ)
- Fewer self-reported respiratory tract infections
- No change in asthma control (ACQ6); FEV_1
- No difference in adverse events (diarrhea more common in azithromycin-treated group)

Concern: selection of antibiotic-resistant bacteria

Gibson PG, et al. *Lancet* 2017; 390:659-68.

Severe Asthma "Survival Kit"

- Peak flow meter
- Nebulizer (or multiple puffs of SABA from MDI)
- Prednisone available at home
- Epi-pen if prior anaphylaxis
- Rapid provider access

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Severe Asthma "Survival Kit"

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Summary from GINA Guidelines -- Patients with Type 2 Inflammation

1. **Assess adherence objectively:**

- Prescribing/dispensing records
- Electronic inhaler monitoring
- Suppression of FeNO with directly-observed therapy

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Summary from GINA Guidelines -- Patients with Type 2 Inflammation

2. Consider clinical Type 2 phenotypes:

- AERD
- ABPA/EGPA
- Chronic rhinosinusitis and/or nasal polyposis
- Atopic dermatitis

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Summary from GINA Guidelines -- Patients with Type 2 Inflammation

3. **Consider increasing the ICS dose** for 3-6 months.

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Summary from GINA Guidelines -- Patients Without Type 2 Inflammation

1. **Consider additional diagnostic investigations:**

- Sputum induction re: inflammatory phenotype
- Chest CT
- Bronchoscopy
- Functional laryngoscopy

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Summary from GINA Guidelines -- Patients Without Type 2 Inflammation

2. Consider trial of non-biologic add-on therapy:

- Tiotropium
- Leukotriene modifier
- Low-dose macrolide (off-label)

Stop ineffective add-on therapies.

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Summary from GINA Guidelines -- Patients Without Type 2 Inflammation

3. **Consider bronchial thermoplasty***

* With registry enrollment.

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