

THE COLLEGE OF  
FAMILY PHYSICIANS  
OF CANADA



LE COLLÈGE DES  
MÉDECINS DE FAMILLE  
DU CANADA

# Practical Talks for Family Docs

March 21, 2023

## Conflict of Interest Disclosure

### **Janice Harvey, MD, CCFP(SEM), FCFP**

- Salary from The College of Family Physician,
- Honoraria/Stipend from McMaster University, OCFP

## Upcoming Webinars – Tuesdays at 12:00 p.m.

**Diagnosis and  
Treatment of ADHD in  
the Child and Youth  
Population in Primary  
Care**

April 18, 2023

Dr. Matt Blackwood

(English)

**Top Research  
Studies of 2022:  
What's new, true  
and poo**

May 2, 2023

Dr. Mike Allan

(English)

**Les grands et petits  
moments de la  
dernière année:**

**Revue de publications  
récentes et de nouveaux  
médicaments**

May 2, 2023

Dr. Nicolas Dugré

(French)

# ADVENTURES & MISADVENTURES IN COPD MANAGEMENT:

## *A Careful Navigation Through Puffer Escalation*

Jamie Falk, PharmD

Kevin Liang, MD, CCFP



# FACULTY/PRESENTER DISCLOSURE

- **Faculty:** Jamie Falk
- **Relationships with financial sponsors:** None to declare



# FACULTY/PRESENTER DISCLOSURE

- **Faculty:** Kevin Liang
- **Relationships with financial sponsors:** None to declare



# OBJECTIVES

*After this session, you should be able to:*

1. Compare the efficacy and harms associated with use of single and multiple inhaled medications in the management of COPD as reported in clinical trials & systematic reviews
2. Apply best evidence, patient characteristics, preferences, and cost considerations to decision making with patients about additional medications and specific devices
3. Determine appropriate monitoring parameters considering symptom reduction and exacerbation prevention when adding or taking away inhaled medications



# STATEMENTS OF THE OBVIOUS...

1. Benefits should be greater than harms
2. Newer isn't necessarily better
3. Only combine things if both are necessary  
Does  $1 + 1 = 2$  or  $<2$  ?  
Does  $1 + 1 + 1 = 3$  or  $<3$  or  $2$  ?





# INFLUENCES IN THE COPD REALM

Clinical Practice  
**GUIDELINES**

Clinical  
**INERTIA**

**INDUSTRY**



**Wanting to do  
SOMETHING**

**COVERAGE**



# CASE 1: BILL...

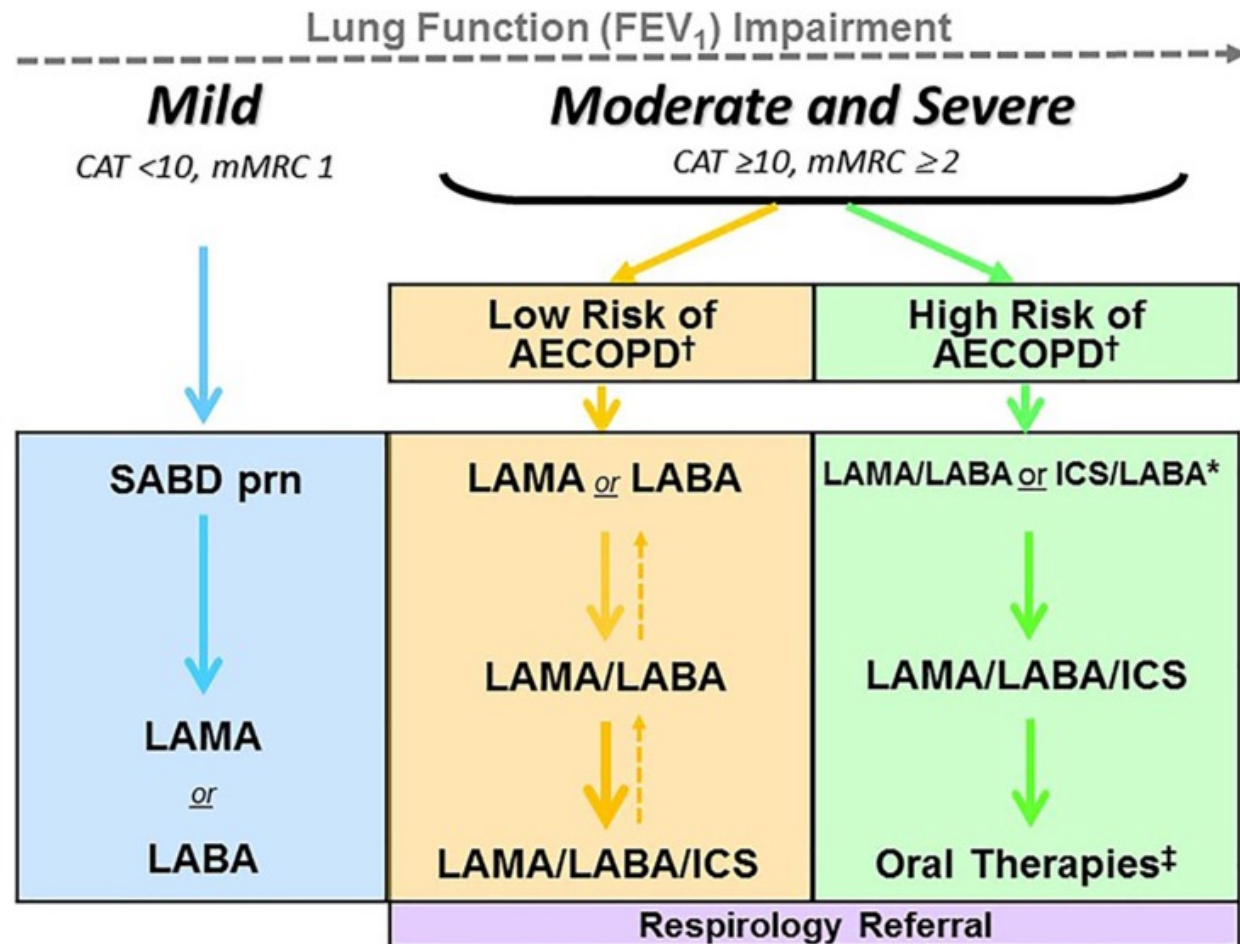
- Bill is a 68-year-old man with a 35-pack year smoking history. He quit smoking 1 year ago when he was diagnosed with COPD. His FEV<sub>1</sub> at the time was 82%.
- His activity is not limited to a great degree, but if his dog picks up the pace when out for a walk, he gets short of breath.
- He finds he needs to use his ipratropium 2 puffs twice a day on most days.

Is Bill on appropriate COPD medication?



# Long-term Management of COPD

CTS 2019 COPD Guidelines Treatment Algorithm



Can J Respir Crit Care Sleep Med 2019



<https://goldcopd.org/2023-gold-report-2/>

- ## 2 BIG QUESTIONS:
- 1) What is gained from step to step?
  - 2) How can we tell if it's helping?

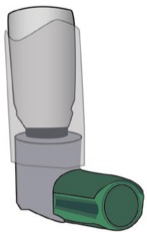
# SABDs: LOTS OF OPTIONS



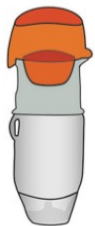
- Salbutamol (q4-6h)



- Terbutaline (q4-6h)



- Ipratropium (q4-6h)



- Ipratropium + Salbutamol (q—6h)



# LET'S START AT THE VERY BEGINNING...

## A VERY QUICK RECAP

2 ways to  
bronchodilate...

1. **SAMA (short-acting muscarinic antagonist (e.g. ipratropium):**

Relaxation of airway smooth muscle by direct inhibition of cholinergic activity

or

2. **SABA (short-acting beta-agonist) (e.g. salbutamol):**

Antagonism of bronchoconstriction via  $\beta_2$ -adrenergic pathways

Does it matter which one you start with?

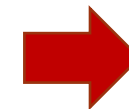
→ Short answer: **NO**

- Onset of action:
  - SAMA <15 minutes
  - SABA <10 minutes
- **SIDE EFFECTS:**
  - SAMA: **dry mouth**, cough, constipation, urinary retention, headache
  - SABA: **tremor**, nervousness, ↑HR, headache

Which profile might be better/worse for your patient?



Do you want to make that a combo, sir?



Combivent  
Respimat?

# Long-term Management of COPD

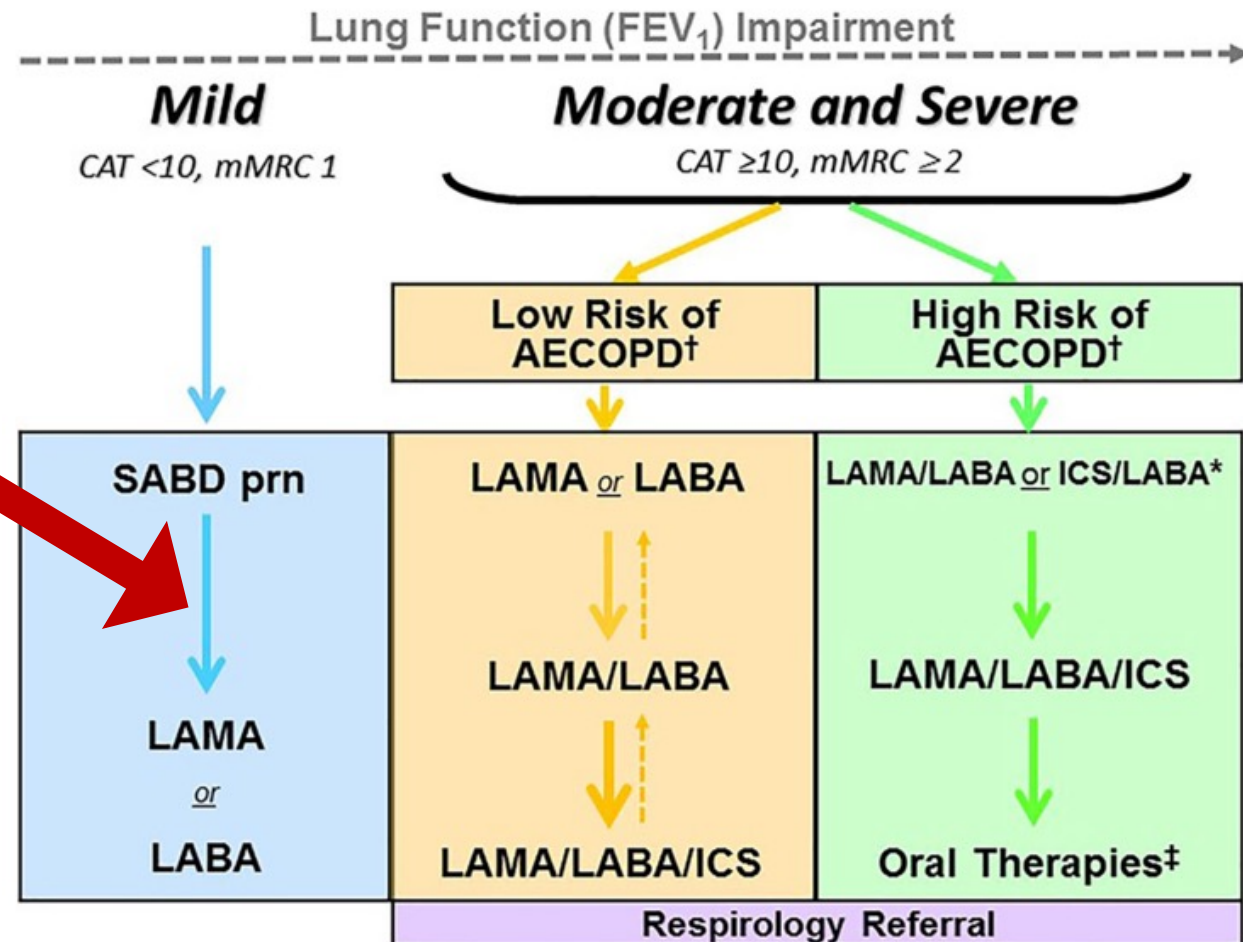
CTS 2019 COPD Guidelines Treatment Algorithm

if patient is using  
SABD regularly  
(no magic threshold)



"...long-acting bronchodilator is the preferred choice except in patients with very occasional breathlessness"

<https://goldcopd.org/2023-gold-report-2/>



# LET'S TAKE A STEP BACK...



What outcomes would be important to you & your patients?

- QoL (how is that defined?)
- Dyspnea
- Activity/Exercise tolerance
- Rescue inhaler use
- Exacerbations (AECOPD)
- Mortality



# A FEW DEFINITIONS...

**Moderate AECOPD:** exacerbation requiring outpatient steroids and/or antibiotics

**Severe AECOPD:** exacerbation requiring hospitalization

**MCID:** minimal clinically important difference





# A FEW DEFINITIONS...

(scores used commonly in COPD clinical trials)

## ■ TDI:

Transition Dyspnea Index **(-9 to +9)** (lower = worse):

Measures changes in dyspnea severity/impact

How much change would you want to see?

- a. 6
- b. 3
- c. 2
- d. 1

**MCID = 1**



# A FEW DEFINITIONS...

(scores used commonly in COPD clinical trials)

## ■ SGRQ:

St. George's Respiratory Questionnaire **(0 to 100)** (higher = worse):

measures impact on overall health, daily life, and perceived well-being

How much change would you want to see?

- a. -20
- b. -10
- c. -5
- d. -2

**MCID = -4**



# CASE 1 CONTINUED...

- Looking over Bill's eChart medication profile, you notice he filled his first and last prescription for one tiotropium inhaler two months ago. When you ask him if he has stopped using it, he replies, "*It wasn't working and it costs too much.*" He has gone back to using his ipratropium.

What are the possible reasons that "*it wasn't working*"?



# NNTs...

(ballpark)

|                        | <b>LAMA or LABA<br/>vs. SABD<br/>(scheduled or prn)</b> |
|------------------------|---|
| ≥ 1 mod-severe AECOPD  | <b>15-20</b>  |
| ≥ 1 severe AECOPD      | <b>35-75</b>  |
| MCID on dyspnea score  | <b>6</b>  |
| MCID on QoL score      | <b>8-10</b>   |
| <b>Adverse events:</b> | <b>NO DIFFERENCE</b>                                    |

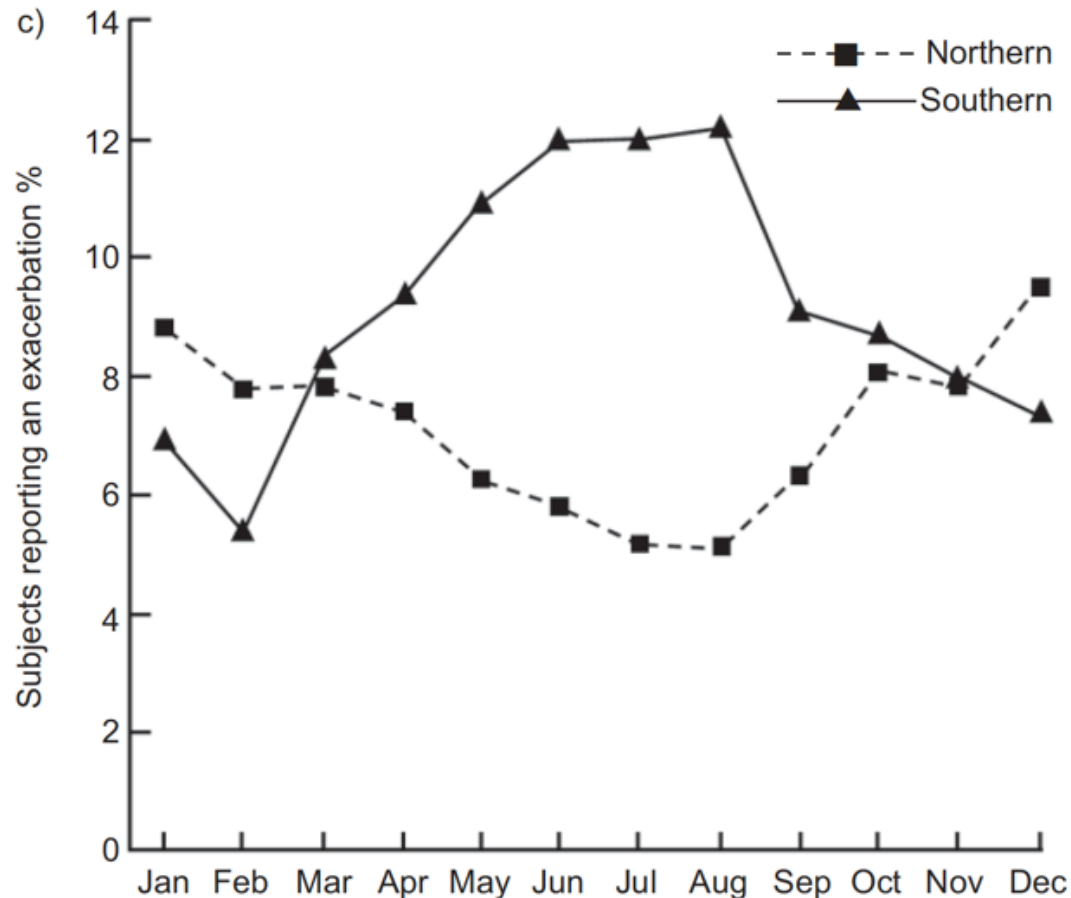
What are the possible reasons that “it wasn’t working”?

- 1) Was it used appropriately?
  - good technique?
  - daily or prn (expecting fast relief?)
- 2) How long was it used for?
- 3) Other illness at the time?
- 4) It actually was no better

(need to make sure 1, 2, & 3 are addressed before we know if 4 is true)



# FLUCTUATIONS



*Eur Respir J* 2012;39:38–45

- Daily and/or weekly symptom variability: 63%
  - **45% during the day**
  - **54% during the week**
- Seasonal symptom variability: **60%**

*Eur Respir J* 2011;37:264–272

How big is the symptom variability compared to the potential effect?



# LABA OR LAMA?

- Overall, the evidence suggests that a LAMA is a tiny bit better:

- $\geq 1$  mod/severe AECOPD **NNT = 33**
- Symptoms (dyspnea, QoL): **no difference**
- Adverse events **very similar**

CDSR 2018, Issue 12. Art. No.: CD012620

What does the latest  guideline recommend?

*Can J Respir Crit Care Sleep Med 2019*

We recommend LAMA monotherapy over LABA monotherapy. **GRADE 1A**

**Practically...** initial choice may come down to:

- 1) patient & clinician preference
- 2) goals of therapy



- **Device type**
- Cost?
- Dosing frequency



# ARE ALL ~~L~~LAMAS CREATED EQUAL?



# LAMAS: LOTS OF OPTIONS



- Glycopyrronium (daily)



- Tiotropium (daily)



- Aclidinium (BID)



- Umeclidinium (daily)

Same goes for  
**LABA** options

Not really, so it depends on:

- **Device type**
- **Cost?**
- **Dosing frequency?**

Does one have the **advantage?**



## RESPIRATORY AGENTS

| Generic Name  | Brand Name<br>(puffs per device) | Strength    | Usual Dosing                     | Cost per<br>Device | Coverage   |      |
|---|----------------------------------|-------------|----------------------------------|--------------------|------------|------|
|   |                                  |             |                                  |                    | Pharmacare | NIHB |
| <b>β<sub>2</sub>-Agonists</b>                       |                                  |             |                                  |                    |            |      |
| <b>Short-acting β<sub>2</sub>-Agonists (SABA)</b>   |                                  |             |                                  |                    |            |      |
| Salbutamol  | Ventolin MDI (200)               | 100mcg      | 2 inh QID (prn)                  | \$6                | Y          | Y    |
| Salbutamol  | Ventolin Diskus (60)             | 200mcg      | 1 inh QID (prn)                  | \$10               | N          | Y    |
| Terbutaline   | Bricanyl Turbuhaler (100)        | 0.5mg       | 1 inh QID                        | \$9                | Y          | Y    |
| <b>Long-acting β<sub>2</sub>-Agonists (LABA)</b>    |                                  |             |                                  |                    |            |      |
| Formoterol  | Foradil Aerolizer (60)           | 12mcg       | 1 inh BID                        | \$55               | Y          | Y-PA |
| Formoterol  | Oxeze Turbuhaler (60)            | 6mcg, 12mcg | 1-2 inh BID (strength dependant) | \$35-47            | Y          | Y-PA |
| Indacaterol   | Onbrez Breezhaler (30)           | 75mcg       | 1 cap daily (inhale twice)       | \$49               | Y          | Y-PA |
| Salmeterol  | Serevent Diskus (60)             | 50mcg       | 1 inh BID                        | \$65               | Y          | Y-PA |
| <b>Anticholinergics</b>                             |                                  |             |                                  |                    |            |      |
| <b>Short-acting Anticholinergics (SAMA or SAAC)</b> |                                  |             |                                  |                    |            |      |
| Ipratropium   | Atrovent (200)                   | 20mcg       | 2 inh QID                        | \$21               | Y          | Y    |
| <b>Long-acting Anticholinergics (LAMA or LAAC)</b>  |                                  |             |                                  |                    |            |      |
| Aclidinium  | Tudorza Genuair (60)             | 400mcg      | 1 inh BID                        | \$56               | Y          | Y    |
| Glycopyrronium                                      | Seebri Breezhaler (30)           | 50mcg       | 1 cap daily                      | \$56               | Y          | Y    |
| Tiotropium  | Spiriva (30)                     | 18mcg       | 1 cap daily                      | \$57               | Y          | Y    |
| Tiotropium  | Spiriva Respimat (60)            | 2.5mg       | 2 inh daily                      | \$57               | Y          | Y    |
| Umeclidinium  | Incruse Ellipta (30)             | 62.5mcg     | 1 inh daily                      | \$53               | Y          | Y    |

# MANITOBA INHALER COSTS

PRICE COMPARISON OF  
COMMONLY PRESCRIBED  
MEDICATIONS IN MANITOBA  
(2022)



Which inhaler devices are you most familiar with? (choose top 3)

- a) Breezhaler
- b) Diskus
- c) Ellipta
- d) Genuair
- e) MDI
- f) Respimat
- g) Turbuhaler



# ASTHMA & COPD: Inhalation Devices Chart

There is no evidence to suggest one device works better than another. Poor inhaler technique: ↓ efficacy. Pt device dissatisfaction: ↓ adherence. Choose device based on pros/cons below & patient preference.

|                    |  |   |  |   |                                       |  |   |   |
|--------------------|--|---|--|---|---------------------------------------|--|---|---|
|                    | beclomethasone <b>QVAR</b><br>ciclesonide <b>ALVESCO</b><br>fluticasone <b>FLOVENT</b><br>formoterol/mometasone <b>ZENHALE</b><br>salmeterol/fluticasone <b>ADVAIR</b><br>ipratropium <b>ATROVENT</b><br>salbutamol <b>VENTOLIN, AIROMIR</b> | olodaterol <b>STRIVERDI</b><br>salbutamol/ipratropium <b>COMBIVENT</b><br>tiotropium <b>SPIRIVA</b><br>tiotropium/olodaterol <b>INSPIOLTO</b> | <b>HandiHaler:</b> tiotropium <b>SPIRIVA</b><br><b>Breezhaler:</b> glycopyrronium <b>SEEBRI</b><br>glycopyrronium/indacaterol <b>ULTIBRO</b><br>indacaterol <b>ONBREZ</b><br><b>Aerolizer:</b> formoterol <b>FORADIL</b> | budesonide <b>PULMICORT</b><br>formoterol <b>OXEZE</b><br>formoterol/budesonide <b>SYMBICORT</b><br>terbutaline <b>BRICANYL</b> | fluticasone propionate <b>AERMONY</b> | fluticasone <b>FLOVENT</b><br>salbutamol <b>VENTOLIN</b><br>salmeterol <b>SEREVENT</b><br>salmeterol/fluticasone <b>ADVAIR</b> | acclidinium <b>TUDORZA</b><br>acclidinium/formoterol <b>DUAKLIR</b> | umeclidinium <b>INCRUSE</b><br>vilanterol/fluticasone <b>BREO</b><br>vilanterol/umeclidinium <b>ANORO</b><br>fluticasone furoate <b>ARNUITY</b><br>fluticasone furoate/vilanterol/umeclidinium <b>TRILEVA</b> |
| <b>DEVICE</b>      | <b>MDI</b>   | <b>Respimat</b>   | <b>HandiHaler, Breezhaler, Aerolizer</b>   | <b>Turbuhaler</b>   | <b>RespiClick</b>                     | <b>Diskus</b>  | <b>Genuair</b>  | <b>Ellipta</b>  |
| <b>Description</b> | Delivers aerosolized stream of medication over ~0.2 seconds.   | Uses a spring to deliver a "soft mist" of medication over ~1.5 seconds.   | Capsules containing medication are pierced, then powder inside is inhaled.   | Dry powder inhaler containing a reservoir of medication.  |                                       |  | Dry powder inhaler containing single dose blisters of medication.   |   |

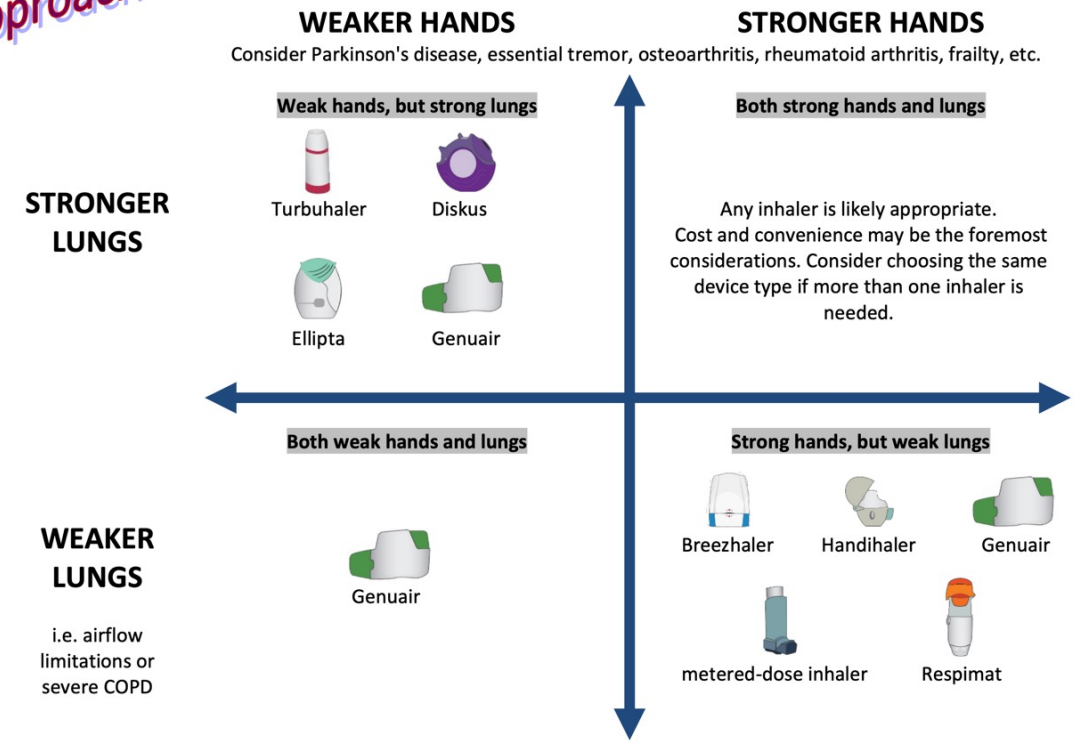
|             |   |  |   |  |
|-------------|---|--|---|--|
| <b>Pros</b> | Low inspiratory flow ≈ 20L/min required<br>• Suitable for all ages. Note: spacer strongly recommended regardless of age (see comments below).<br>• Spacer with a mask available for cognitive impairment, frail, < 5yrs old, etc. | • Slower actuation may improve technique vs MDI<br>• <b>DOSE COUNTER:</b> numbered by interval (frequency of interval varies by medication); loading base locks to signal empty<br>• <b>COMBIVENT Respimat</b> has cost advantage over | • Rattling or whirring heard if capsule's contents inhaled correctly. Can look to view empty capsules (and Breezhaler has clear capsules).<br>• Low inspiratory effort needed<br>• <b>DOSE COUNTER:</b> each capsule equals 1 dose; thus no dose counter required | • Dose is not lost even if base is twisted multiple times; however, dose counter will no longer be accurate<br>• <b>DOSE COUNTER:</b> every 20 <sup>th</sup> dose numbered to give |
|             | • Can be used with mechanical ventilation (e.g. in critical care units)   |  |   |  |

|             |  |   |   |   |
|-------------|--|---|---|---|
| <b>Cons</b> | • <b>DOSE COUNTER:</b> most devices lack dose counter (exceptions: <b>ADVAIR, ZENHALE</b> )<br>• Spacer can be cumbersome; however, if using only at home in the morning/evening, burden is low.<br>• Susceptible to freezing<br>• Requires priming (x 4 sprays) if not used for ≥ 5 days.<br>• May add to carbon footprint. <sup>Wilkinson<sup>19</sup></sup> | • Respiration...<br>• In...<br>• N...<br>• N...<br>• R...<br>• R...<br>• R... | • Respiration...<br>• In...<br>• N...<br>• N...<br>• R...<br>• R...<br>• R... | • Respiration...<br>• In...<br>• N...<br>• N...<br>• R...<br>• R...<br>• R... |
|             |  | (COMBIVENT) or ≥ 7 days (SPIRIVA/INSPIOLTO).                                  |   | ...drug in reservoir  |

What factors do you consider?  
 Are strong hands & dexterity an important consideration for your patients?  
 What about inspiratory ability?  
 What about cognitive ability?  
 What about environmental impact?

The HANDS vs LUNGS Approach

## How to Pick an Inhaler for a COPD patient



# ADHERENCE FACTORS

- Up to **50%** of patients have poor technique
- Adherence rates in clinical trials:
  - as high as **70%-90%**
- Adherence rates in clinical practice:
  - as low as **10-30%!**

*At each assessment...*



## 1. Inhaler Technique

Ask if they have trouble  
Get them to show you  
(or refer to their pharmacist)



## 2. Adherence to ICS

Ask your patient  
Check Rx profile



# CASE 2: JOAN...

Joan is a 78-year-old patient who has had her COPD managed for the last year on Glycopyrronium (LAMA) with some degree of effectiveness. However, she's finding that she can no longer do her grocery shopping without having to use multiple doses of her salbutamol.

What other questions do we have?

What are possible next steps for Joan?

- Other activities that make you short of breath?
- Other diagnoses?
- Bad season?
- Adequate inspiratory flow?
- Change in dexterity/strength?



# ARE 2 BETTER THAN 1?



Relaxation of airway smooth muscle by direct inhibition of cholinergic activity (**LAMA**)

+

Antagonism of bronchoconstriction via  $\beta$ 2-adrenergic pathways (**LABA**)



Better effect?



# LAMA+LABA COMBOS



- Glycopyrronium (LAMA) + Indacaterol (LABA) (daily)



- Umeclidinium (LAMA) + Vilanterol (LABA) (daily)



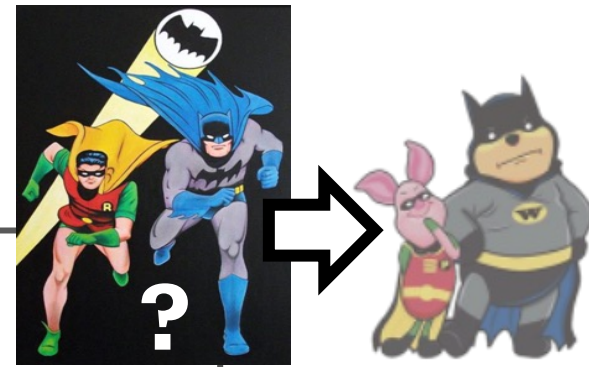
- Aclidinium (LAMA) + Formoterol (LABA) (BID)



- Tiotropium (LAMA) + Olodaterol (LABA) (daily)

Do they offer an **advantage** over **single** ingredients alone?

# PUTTING THE DYNAMIC DUO TO THE TEST



**>25 RCTs:**  
**LAMA or LABA**  
 vs.  
**LAMA + LABA**

*How do they feel?*

RESULTS

- **Having 1 or more exacerbations:**
  - **NNT = 40-42** X 3-12 months
  - **NO DIFFERENCE** in hospitalizations

|                       | DYSPNEA (TDI)                         | QoL (SGRQ)                            |
|-----------------------|---------------------------------------|---------------------------------------|
| Mean score change     | <b>0.2 – 0.5</b><br><b>(MCID = 1)</b> | <b>1.2 – 1.7</b><br><b>(MCID = 4)</b> |
| NNT (to achieve MCID) | <b>10 – 20</b>                        | <b>9 – 17</b>                         |

- **Rescue puffs: ~1/2 puff/day less**
- **Adverse events (any overall or serious):**
  - **No difference** ✓

CDSR 2018, Issue 12. Art. No.: CD012620  
 CDSR 2015, Issue 10. Art. No.: CD008989  
 Respir Res 2017;18(1):196  
 Int J COPD 2017;12:1867-76  
 Int J COPD 2017;12:907-922  
 Chest 2016;149(5):1181-96  
 Thorax 2016;71(1):15-25





**SO FAR...**

# NNTs... diminishing returns (ballpark)



|                       | <b>LAMA or LABA<br/>vs. SABD<br/>(scheduled or prn)</b> |                      | <b>LAMA+LABA<br/>vs. LAMA or LABA</b> |
|-----------------------|---|----------------------|---------------------------------------|
| ≥ 1 mod-severe AECOPD | <b>15-20</b>  |                      | <b>40</b>                             |
| ≥ 1 severe AECOPD     | <b>35-75</b>  | ➔                    | <b>no diff</b>                        |
| MCID on dyspnea score | <b>6</b>  |                      | <b>10-20</b>                          |
| MCID on QoL score     | <b>8-10</b>   |                      | <b>10-15</b>                          |
| Adverse events:       |   | <b>NO DIFFERENCE</b> | <b>✓</b>                              |

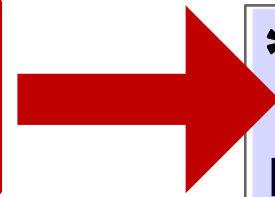
# UNDERTAKING A COMBO TRIAL

- Assuming Joan has had improvement on one of the therapies (she has had some benefit with a LAMA)...
- What is an **adequate trial** of a second ingredient?



What are our/patient's **desired outcomes**?

- Dyspnea
- Activity tolerance
- Rescue inhaler use



\* Ease of assessment?  
Benefits seen early  
(**2-4** weeks?)

- QOL



Multifactorial; takes longer to determine; subjective

- Exacerbations/hospitalizations



May take years to determine; baseline events not reliable

How big is the symptom variability compared to the (now smaller) potential effect?



If successful, a combo inhaler is much less expensive than two separate inhalers. \$\$\$

If not successful, 



\$65-90 vs. \$110-120

# CASE 3: ROGER...

## ICS (inhaled corticosteroid):

Theory: ↓ **inflammation**

→ Key therapy in asthma

→ Inflammation in COPD?  
- Yes, so it should help, right?

- Roger has recently finished a course of antibiotics for a respiratory tract infection that led to AECOPD (his only one this year). He's generally doing better.
- He is currently using the Anoro Elipta (LABA+LAMA). He just saw a commercial for Trelegy (LABA+LAMA+**ICS**) (something about a guy who can bring his wife flowers because of well-controlled COPD). He asks you if this would be a good thing for him.



Individual results may vary. ←

<https://www.trelegy.com>

**What else do we want to know about Roger?**



# MORE IS ALWAYS BETTER, RIGHT?

## Gillette Introduces New 27 Blade Razor

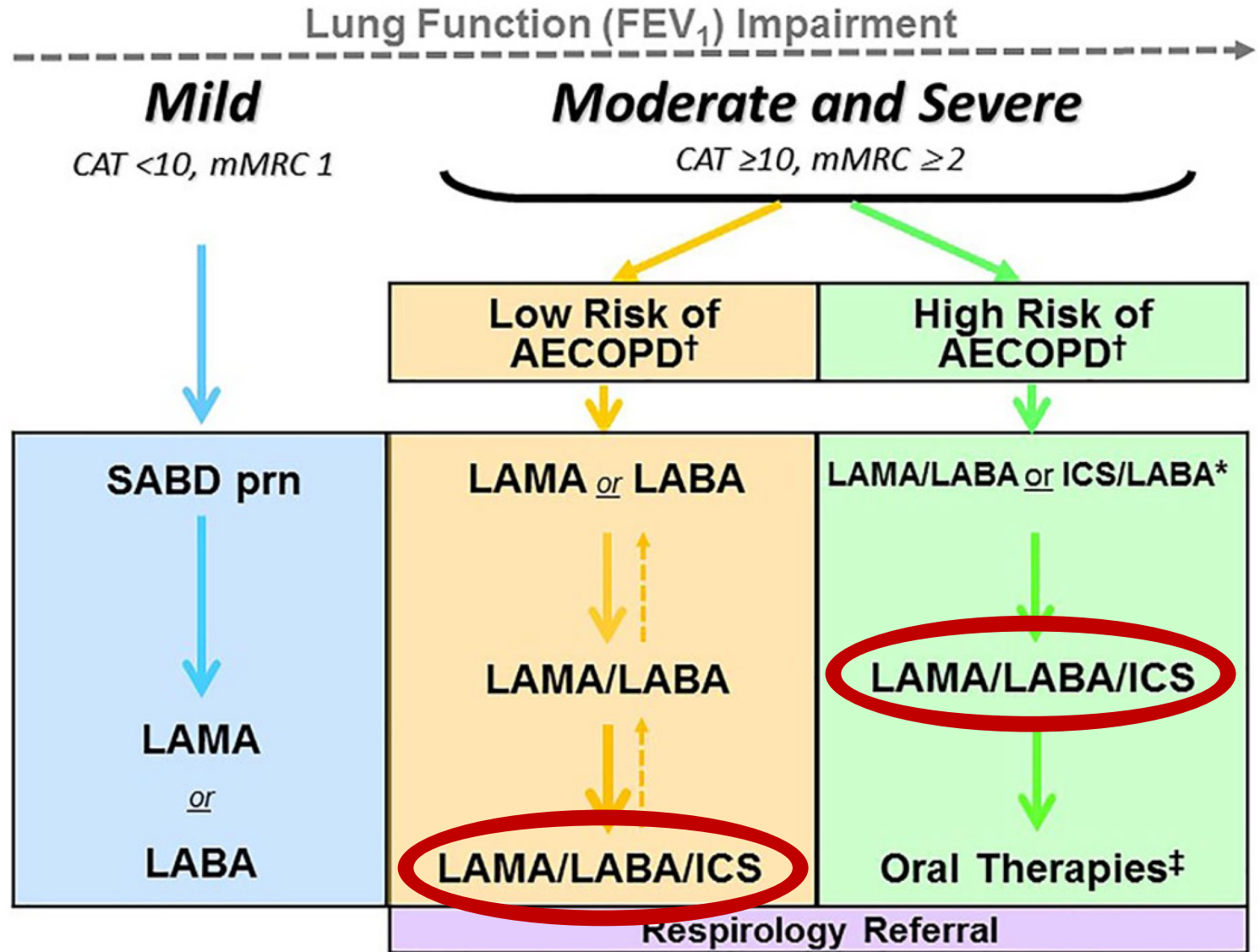
By *Ben Dungan* on February 1, 2019 · *No Comment*

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# SHOULD WE GO "ALL IN"?

Guidelines say YES!



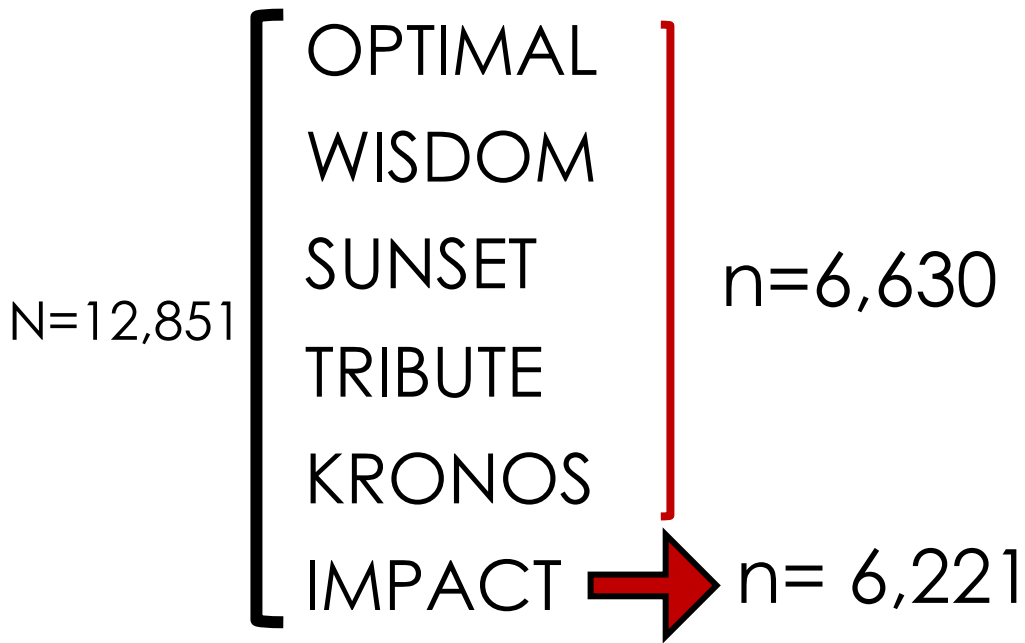
What is the number of moderate/severe AECOPD saved per year that you'd consider important (e.g. for your patients who have 1-2 AECOPDs per year like Roger)



- a) 2
- b) 1
- c) 0.5 (i.e. 1 saved in 2 yrs)
- d) 0.2 (i.e. 1 saved in 5 years)



# NOTABLE TRIPLE TRIALS:



*N Engl J Med* 2018;378:1671-80  
Once-Daily Single-Inhaler **Triple versus Dual** Therapy in Patients with COPD

**WHO?** FEV1 = 45%,  $\geq 1$  AECOPD/yr (55% had  $\geq 2$ ), mean age = 65

**What did they find @ 1yr?**

→ ↓ mod-severe AECOPD = **0.3/patient/yr**  
(or ~1 **event saved in 3 yrs**)

→ ↓ hospitalizations = **0.06/patient/yr**

→ ↓ mortality = **0.8% (NNT = 120)**

Did patients **FEEL BETTER?** → **well...**

→ SGRQ -1.8 → NNT MCID = 8

→ TDI change **not reported** → ?

IMPACT? → yes, a bit →

What's the CATCH?

#1

#2

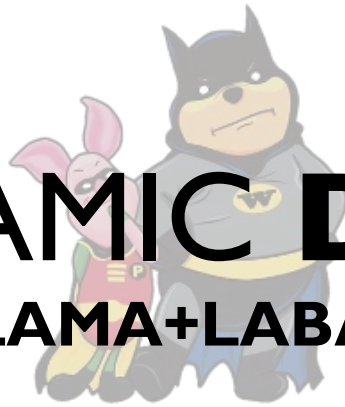
- you could have history of **ASTHMA**
- **80% on ICS** pre-randomization ✖

**NNH (pneumonia) = 34**

~40% on triple

# DYNAMIC DUO vs. TRIPLE THREAT

(LAMA+LABA) (LAMA+LABA+ICS)



## 3 meta-analyses:

- Reduction in **AECOPD** (Cazzola, *Eur Resp J* 2018)  
NNT = **39** (for triple) 👍
- Increase in **PNEUMONIA** (Zheng, *BMJ* 2018; Zayed, *Clin Respir J* 2019)  
NNH = **38-39** (against triple) 👎

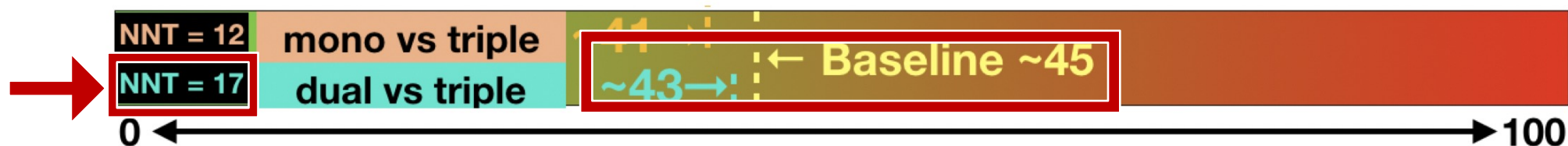
But, did they at least **feel better** day-to-day?



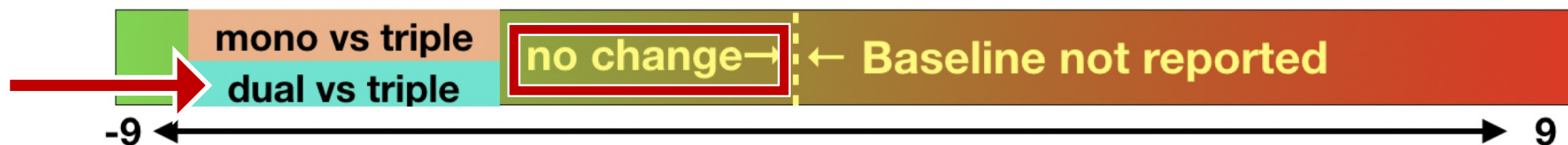
# Short answer... NO

## Ballpark estimates of the benefits seen from inhalers on clinically important outcomes

St George's Respiratory Questionnaire - MCID = - 4  
(NNT to reach MCID)



Transition Dyspnea index - MCID = -1



Rescue inhaler puffs per day



# NNTs... diminishing returns? (ballpark)

any real  
net benefit?

|                       | LAMA or LABA<br>vs. SABD<br>(scheduled or prn) | LAMA+LABA<br>vs. LAMA or LABA | LAMA+LABA+ICS<br>vs.<br>LAMA+LABA |
|-----------------------|--|-------------------------------|-----------------------------------|
| ≥ 1 mod-severe AECOPD | 15-20  | 40                            | 38                                |
| ≥ 1 severe AECOPD     | 35-75  | NS                            | 0.06 less/pt/yr                   |
| MCID on dyspnea score | 6  | 10-20                         | NA                                |
| MCID on QoL score     | 8-10   | 10-15                         | 17                                |

Adverse events: **NO DIFFERENCE** **Pneumonia: 39**

**BUT  
WAIT!**

- Other AEs?
- thrush
  - dysphonia
  - osteoporosis

# IMPACT ETHOS

N Engl J Med June 24, 2020;383:35-48

## Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD

**WHO?** FEV1 = 43%,  $\geq 1$  AECOPD/yr (57% had  $\geq 2$ ), **mean age = 65**

**WHAT?** **LABA+LAMA+ICS** (budesonide 320mcg or 160mcg) vs. **LABA+LAMA** vs. **ICS+LABA**

### What did they find @ 1 yr?

→ ↓ mod-severe AECOPD = **0.35/pt/yr** (or ~1 saved in 3 yrs)

→ ↓ hospitalizations = **no difference**

→ ↓ mortality = **1.0%** (NNT=100)

Did patients **FEEL BETTER?** → **well...**

→ SGRQ change **-1.5 to -1.9** → NNT MCID = **13-15**

→ TDI change **0.4** (both doses) @24 wks (recall MCID =1)

EFFICACY IN CONTEXT  
OF OTHER TRIPLE  
TRIALS... **VERY SIMILAR**

What's the  
CATCH?

#1

- you could have history of **ASTHMA**
- **80% on ICS** pre-randomization

#2

**NNH (pneumonia) = 59**

~40% on triple





DEC 18, 2020

Episode 467: COPD inhalers – the evidence leaves you gasping for breath - PART III

In episode 467, Mike and James finish off talking with Jamie Falk about COPD/inhalers. We go over the some of the latest trials for the triple therapies and then wrap up all the evidence into a nice package and put a bow on it. At the end we finally get to the issue of eosinophils and let you know if you need to know this number. Show notes

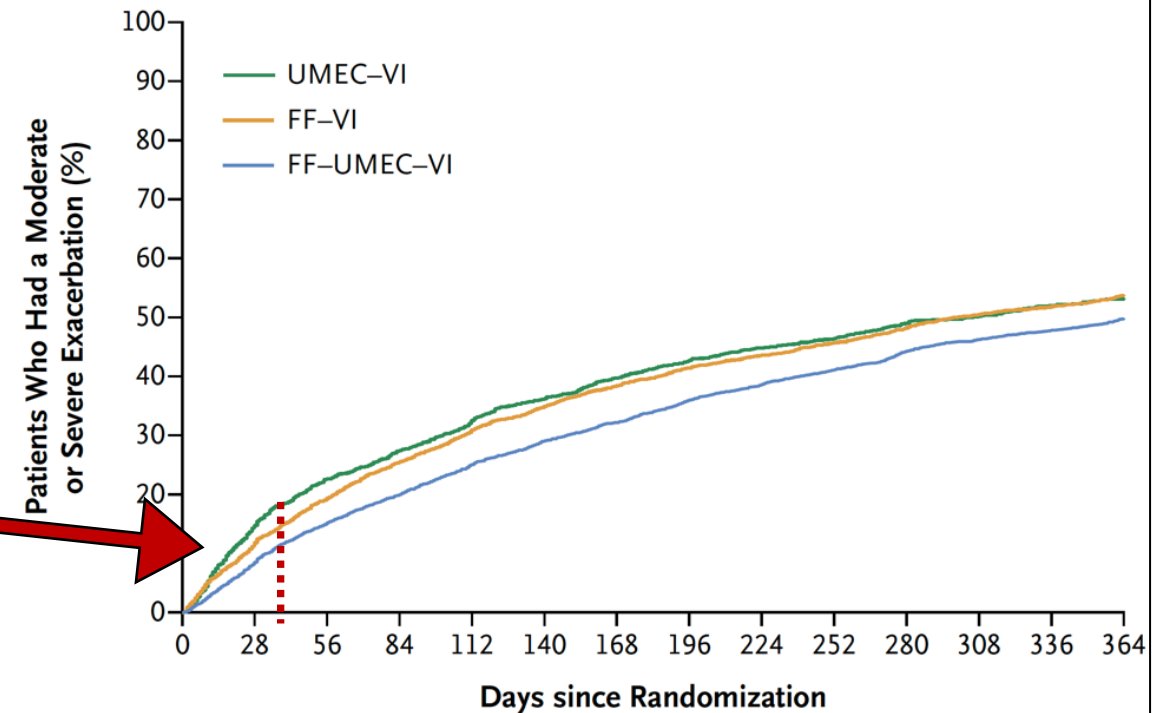
# IMPACT:

## EFFECT OF ICS USE AT BASELINE ON **AECOPD**

“...more than 70% were receiving an ICS, and patients with a history of asthma were included. Thus, for the patients assigned to **the LAMA+LABA group, many of whom were actually stepping down in their treatment, ICS were abruptly withdrawn at the time of randomization...**

This design peculiarity, compounded by the probable inclusion of some patients who **could have met a standard case definition of asthma**, could explain the **rapid surge in exacerbations observed in the first month** after randomization in the LAMA-LABA group; during the subsequent 11 months of follow-up, the incidence of exacerbation with LAMA-LABA was practically identical to that with triple therapy.”

Time-to-First-Event Analysis



IMPACT trial: NEJM 2018;378:1671-80

i.e. the benefit seen in the RCT is likely the best case scenario

FDA, Aug 31, 2020...

**VOTE:** Do the data from the IMPACT trial provide substantial evidence of efficacy to support the claim that TRELEGY ELLIPTA improves all-cause mortality in patients with COPD?

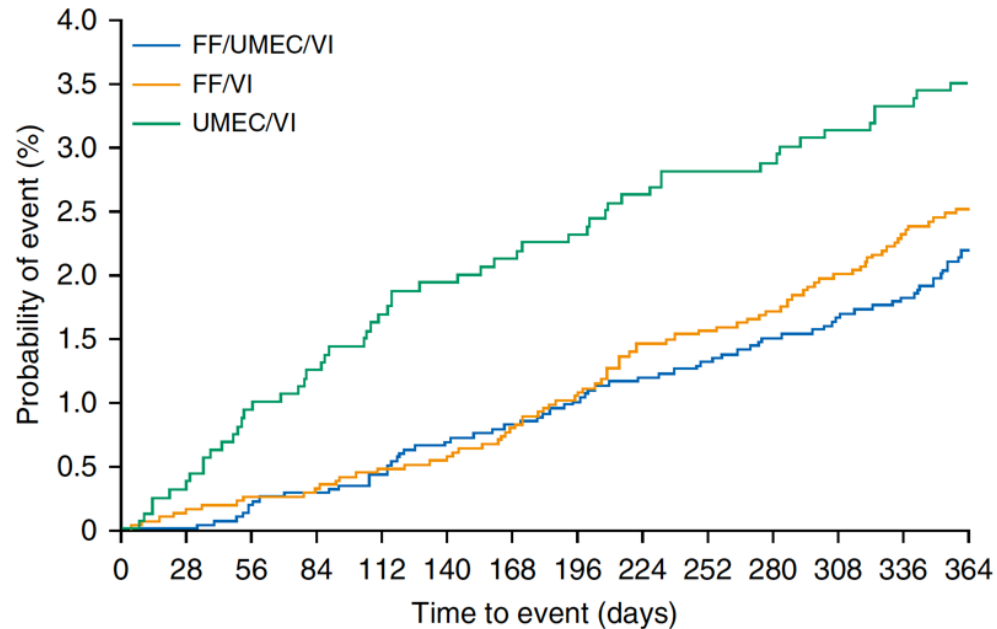
**Vote Result:** Yes: 1 **No: 14** Abstain: 0

# IMPACT:

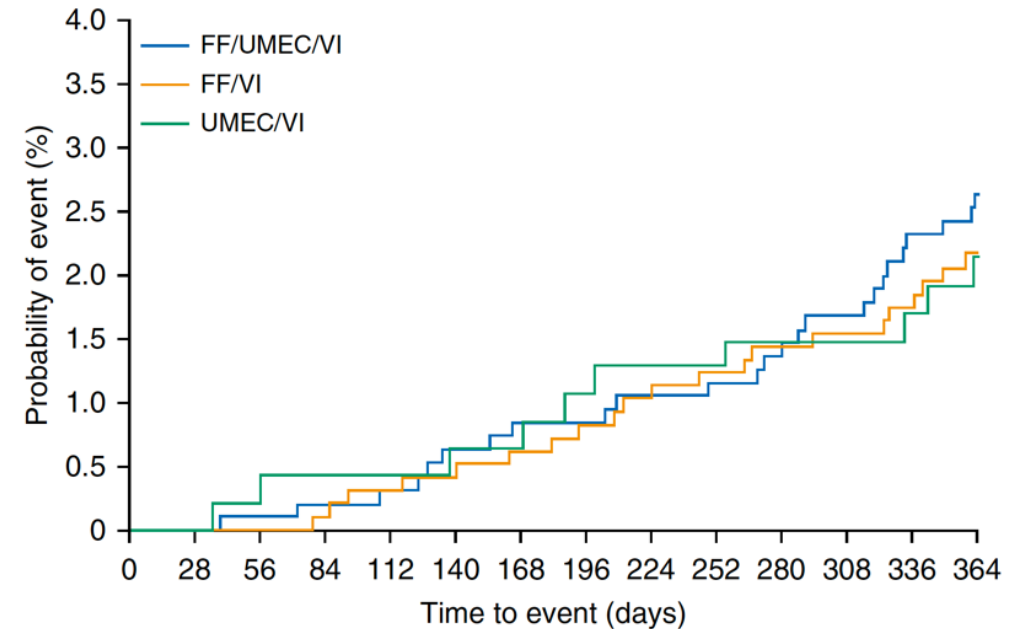
## EFFECT OF ICS USE AT BASELINE ON **MORTALITY**

ICS at screening **inappropriate RCT starting point**

No ICS at screening **appropriate RCT starting point**



|            |       |       |       |       |       |
|------------|-------|-------|-------|-------|-------|
| FF/UMEC/VI | 3,202 | 3,190 | 3,172 | 3,154 | 3,024 |
| FF/VI      | 3,158 | 3,147 | 3,130 | 3,103 | 2,941 |
| UMEC/VI    | 1,600 | 1,579 | 1,562 | 1,546 | 1,474 |

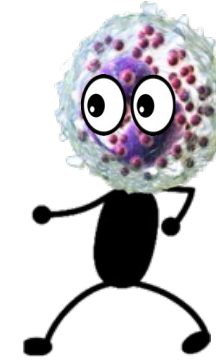


|            |     |     |     |     |     |
|------------|-----|-----|-----|-----|-----|
| FF/UMEC/VI | 949 | 947 | 941 | 938 | 895 |
| FF/VI      | 976 | 971 | 965 | 957 | 907 |
| UMEC/VI    | 470 | 466 | 465 | 462 | 440 |

**Similar pattern seen in ETHOS...**

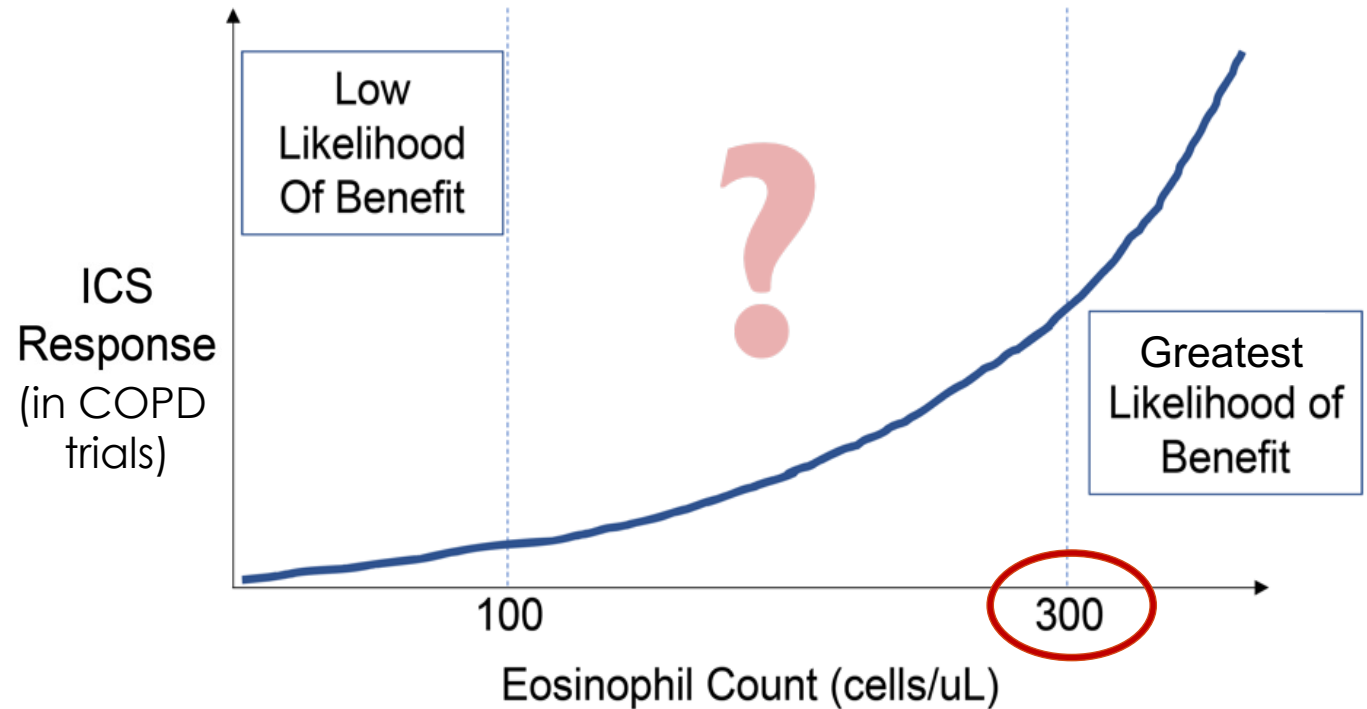
*Am J Respir Crit Care Med* Articles in Press, Nov 30, 2020

# HEY, EOSINOPHILS... WHAT CAN YOU TELL US?



Why might they be important  
in **COPD** pathophysiology?

- **Airway eosinophilia**
  - a hallmark inflammatory response in asthma
  - involved in COPD airway inflammatory process
- **Blood eosinophil** counts might reflect degree of **sputum eosinophilia** (increased in some patients with AECOPD)



# Number Needed to Treat to Prevent an Acute Exacerbation

## ICS/LABA/LAMA vs LABA/LAMA

|           | Overall NNT | NNT Eosinophils <300 | NNT Eosinophils ≥300 |
|-----------|-------------|----------------------|----------------------|
| 3 months  | 20          | 61                   | 8                    |
| 6 months  | 24          | 61                   | 11                   |
| 12 months | 39          | 47                   | 9                    |

Stolen shamelessly from J Leung (BSMC 2019)

Breztri  
(budesonide  
glycopyronium  
formoterol)



Trelegy  
(fluticasone  
umeclidinium  
vilanterol)



# HOW MUCH BETTER MIGHT IT BE?



**BUT...** no clinically important differences in QoL or dyspnea scores in the IMPACT study if >300  
**AND...** no effect of eosinophil count on rates of pneumonia

Cost... **\$135-145/month (triple)** vs. **\$60-90/month (dual)**

# THE GOLD 2023 APPROACH

<https://goldcopd.org/2023-gold-report-2/>

## ▶ FACTORS TO CONSIDER WHEN INITIATING ICS TREATMENT

Factors to consider when initiating ICS treatment in combination with one or two long-acting bronchodilators (note the scenario is different when considering ICS withdrawal):



| · STRONG SUPPORT ·  | · CONSIDER USE ·   | · AGAINST USE ·   |
|---|--|---|
| <ul style="list-style-type: none"><li>• History of hospitalization(s) for exacerbations of COPD#</li><li>• ≥ 2 moderate exacerbations of COPD per year#</li><li>• Blood eosinophils &gt;300 cells/μL</li><li>• History of, or concomitant, asthma</li></ul> | <ul style="list-style-type: none"><li>• 1 moderate exacerbation of COPD per year#</li><li>• Blood eosinophils 100-300 cells/μL</li></ul> | <ul style="list-style-type: none"><li>• Repeated pneumonia events</li><li>• Blood eosinophils &lt;100 cells/μL</li><li>• History of mycobacterial infection</li></ul> |

#despite appropriate long-acting bronchodilator maintenance therapy (see Table 3.4 and Figure 4.3 for recommendations);

\*note that blood eosinophils should be seen as a continuum; quoted values represent approximate cut-points; eosinophil counts are likely to fluctuate.





# THERE ARE A LOT OF “IFs”: YOU GOTTA HAVE FAITH (OR HOPE)?

## 2 possible approaches:

### 1) PREVENTATIVE

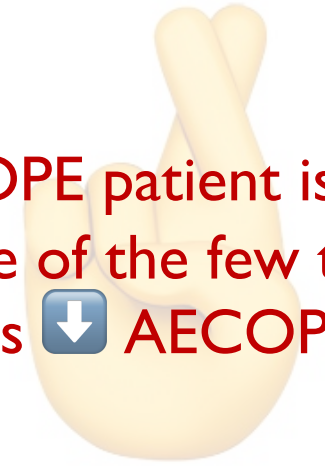
→ prescribe knowing that AECOPD are reduced overall

Keeping  
in mind...

- AECOPD occur relatively infrequently
- seasonal fluctuations not uncommon



HOPE patient is  
one of the few that  
gets ↓ AECOPD



### 2) SYMPTOM-based

→ prescribe the inhaler → assess if patient feels better

Problems...

- COPD symptoms often fluctuate widely day-to-day/wk-to-wk (often > than differences seen in RCTs)
- When are new inhalers started? → when patient feels worse



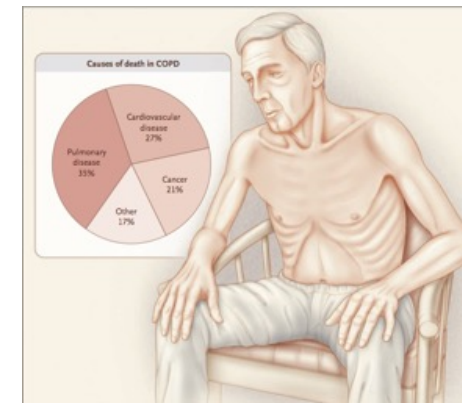
Difficult or  
impossible to  
determine



# WHAT ELSE SHOULD WE DO?



- Smoking cessation
- Up to date vaccinations
- Pulmonary rehab
- CVD risk reduction
- Continually track adherence and technique





# QUESTIONS ?



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