



GRASPING AT STRAWS & GASPING AT FLAWS:

a deep dive into COPD puffer escalation

EK CPD Winter Conference

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of Manitoba**

FACULTY/PRESENTER DISCLOSURE

- Faculty: **Jamie Falk**
- Relationships with commercial interests: none
- Grants/Research Support: none
- Speakers Bureau/Honoraria: none
- Other:
 - Employee of the University of Manitoba
 - member of PEER (non-salaried)



OBJECTIVES

1. Compare and contrast the **efficacy and harms associated with use of single and multiple inhaled medications** in the management of COPD
2. Apply best evidence, patient characteristics, and preferences to the **decision making** around additional COPD therapies and the determination of **reasonable monitoring parameters**
3. Examine **the effects of COPD inhalers on climate change** and the **effects of climate change on patients with COPD**

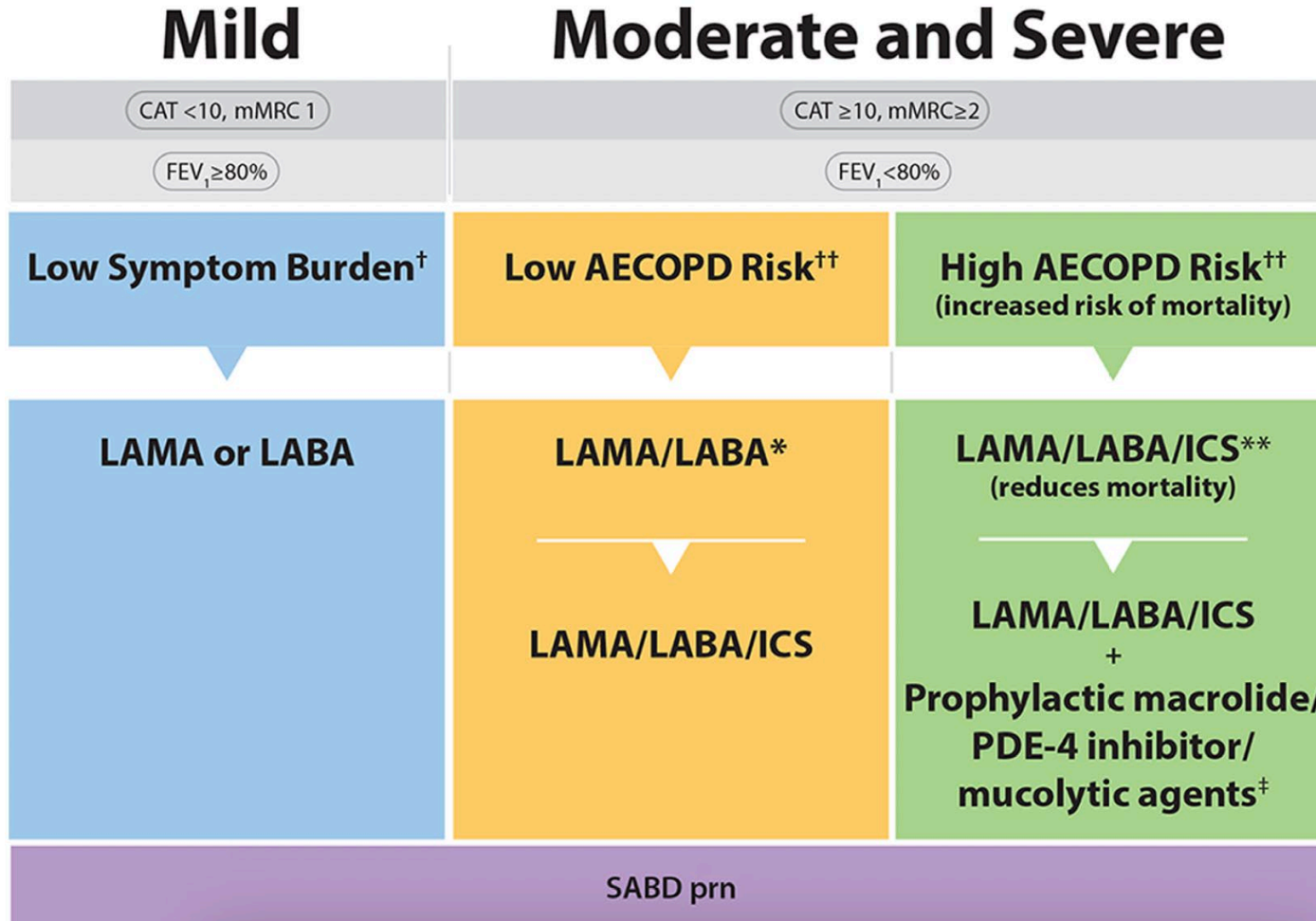


Long-term Management of COPD

CTS 2023 COPD Guidelines Treatment Algorithm



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

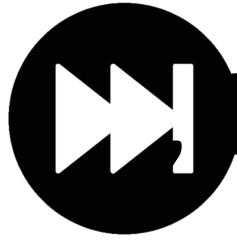


2 BIG

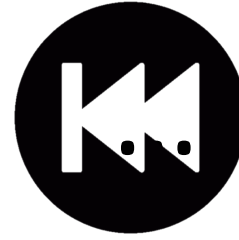
QUESTIONS:

- 1) What is gained from step to step?
- 2) How can we tell if the intervention is helping?

BEFORE WE



LET'S



What outcomes are important to us/our patients?

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



A FEW DEFINITIONS...

- **Moderate AECOPD:** exacerbation requiring outpatient steroids and/or antibiotics
- **Severe AECOPD:** exacerbation requiring hospitalization
- **MCID:** **m**inimal **c**linically **i**important **d**ifference

TDI: Transition Dyspnea Index (-9 to +9) → MCID = **1**

SGRQ: St. George's Respiratory Questionnaire (0 to 100) → MCID = **-4**

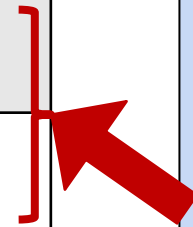


NNTs... (ballpark)

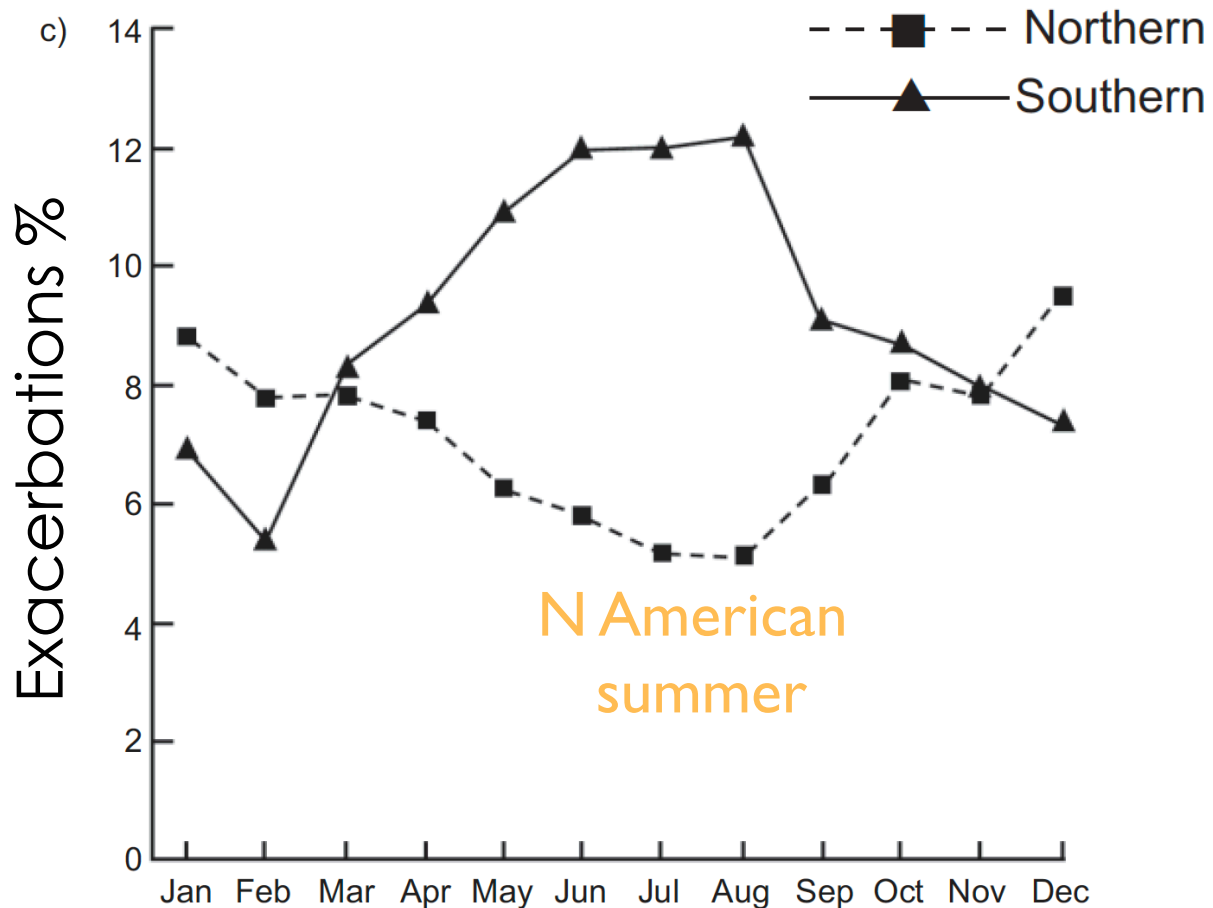
	LAMA or LABA vs. SABD (scheduled or prn)
≥ 1 mod-severe AECOPD	15-20
≥ 1 severe AECOPD	35-75
MCID on dyspnea score	6
MCID on QoL score	8-10
Adverse events:	NO DIFFERENCE

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

- 1) Not used appropriately?
 - technique?
 - prn vs daily (expecting fast relief?)
- 2) How long was it used for?
- 3) Other illness at the time?
- 4) **Bad week, bad season**
- 5) It was truly no better



FLUCTUATIONS



Eur Respir J 2012;39:38–45

- Daily and/or weekly symptom variability: **63%**
- Seasonal symptom variability: **60%**

Eur Respir J 2011;37:264–272

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

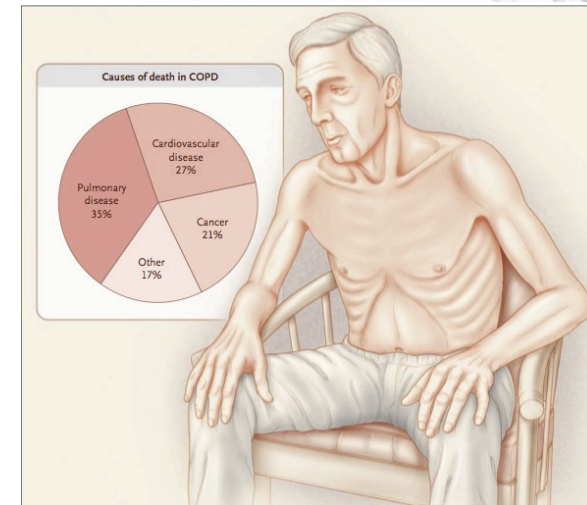


THROW SOME POLLUTION INTO THE MIX...

Air pollution and COPD: GOLD 2023 committee report

Eur Respir J 2023; 61: 2202469

- **Exposure:**
 - *Acutely:* exacerbates symptoms and reduces lung function
 - *Chronically:* increased risk of getting COPD and accelerated lung function decline
- **Air pollution attributable mortality:**
 - WHO (2012): 8% of global COPD mortality
 - China (2015): 12% of pollution-related mortality were COPD deaths
 - Washington state (2006-2017): COPD mortality increased 14% during wildfire smoke-filled days
 - >50% of excess mortality related to air pollution is CV in nature
 - preferentially affects COPD patients due to high CVD prevalence?



LABA OR LAMA?

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

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

Can J Respir Crit Care Sleep Med 2023;7(4):173-191 (Suppl 2)
 CDSR 2018, Issue 12. Art. No.: CD012620



My first choice: **LAMA**

Reason 1:

Reason 2: SABA is the rescue → non-HFA option (terbutaline)

Mild	Moderate and Severe	
CAT <10, mMRC 1	CAT ≥10, mMRC ≥2	
FEV ₁ ≥80%	FEV ₁ <80%	
Low Symptom Burden [†]	Low AECOPD Risk ^{††}	High AECOPD Risk ^{††} (increased risk of mortality)
LAMA or LABA	LAMA/LABA*	LAMA/LABA/ICS** (reduces mortality)
	LAMA/LABA/ICS	LAMA/LABA/ICS + Prophylactic macrolide/ PDE-4 inhibitor/ mucolytic agents [‡]
SABD prn		

SHORT-ACTING RELIEF vs. LONG-LASTING CLIMATE EFFECT?

		Inhaler type	Driving distance (km) per 200 doses 	Cost per 200 doses 
SABA	Salbutamol	MDI (high-volume HFA) e.g. Ventolin, Apo, Sanis	137 685	6
	Salbutamol	MDI (low-volume HFA) e.g. Teva	47 235	6
	Terbutaline	Turbuhaler	4 20	18
SAMA	Ipratropium	MDI	71 355	22

Average mod-severe COPD trial patient: 2.5-3 puffs/day = ~1000 puffs/yr...

ARE ALL ~~LLAMA~~s CREATED EQUAL?



LAMAs: LOTS OF OPTIONS



- Glycopyrronium



- Tiotropium

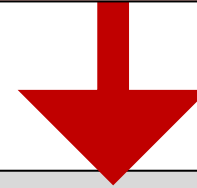


- Aclidinium



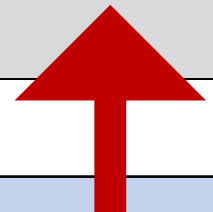
- Umeclidinium

Same goes for **LABA** options



Not really, so it depends on:

- **Device type**
- Cost? (all ~\$55/month)
- Dosing frequency? **OD-BID**
- Eco: **similar**



Does one have the **advantage?**

ARE 2 BETTER THAN 1?



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

+

Antagonism of bronchoconstriction via β 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?

so far...

NNTs... diminishing returns (ballpark)



	LAMA or LABA vs. SABD (scheduled or prn)	LAMA+LABA vs. LAMA or LABA
≥ 1 mod-severe AECOPD	15-20	12-44 (NS)
≥ 1 severe AECOPD	35-75	53 (NS)
MCID on dyspnea score	6	12
MCID on QoL score	8-10	23
Adverse events:	NO DIFFERENCE ✓	

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

CASE: ROGER...

- Roger recently finished a course of antibiotics for AECOPD (his only one this year). He's generally doing better but continues to have activity-limiting shortness of breath.
- He's currently using the Anoro Elipta (LABA+LAMA), but just saw a commercial for Trelegy (LABA+LAMA+**ICS**) (something about a guy who can now bring his wife flowers). He asks you if this would be a good thing for him.



Individual results may vary.



<https://www.trelegy.com>

ICS (inhaled corticosteroid):

↓ inflammation...

→ Key therapy in **asthma**

→ Inflammation in **COPD?**

- Some, so it should help, right?

MORE IS ALWAYS BETTER, RIGHT?

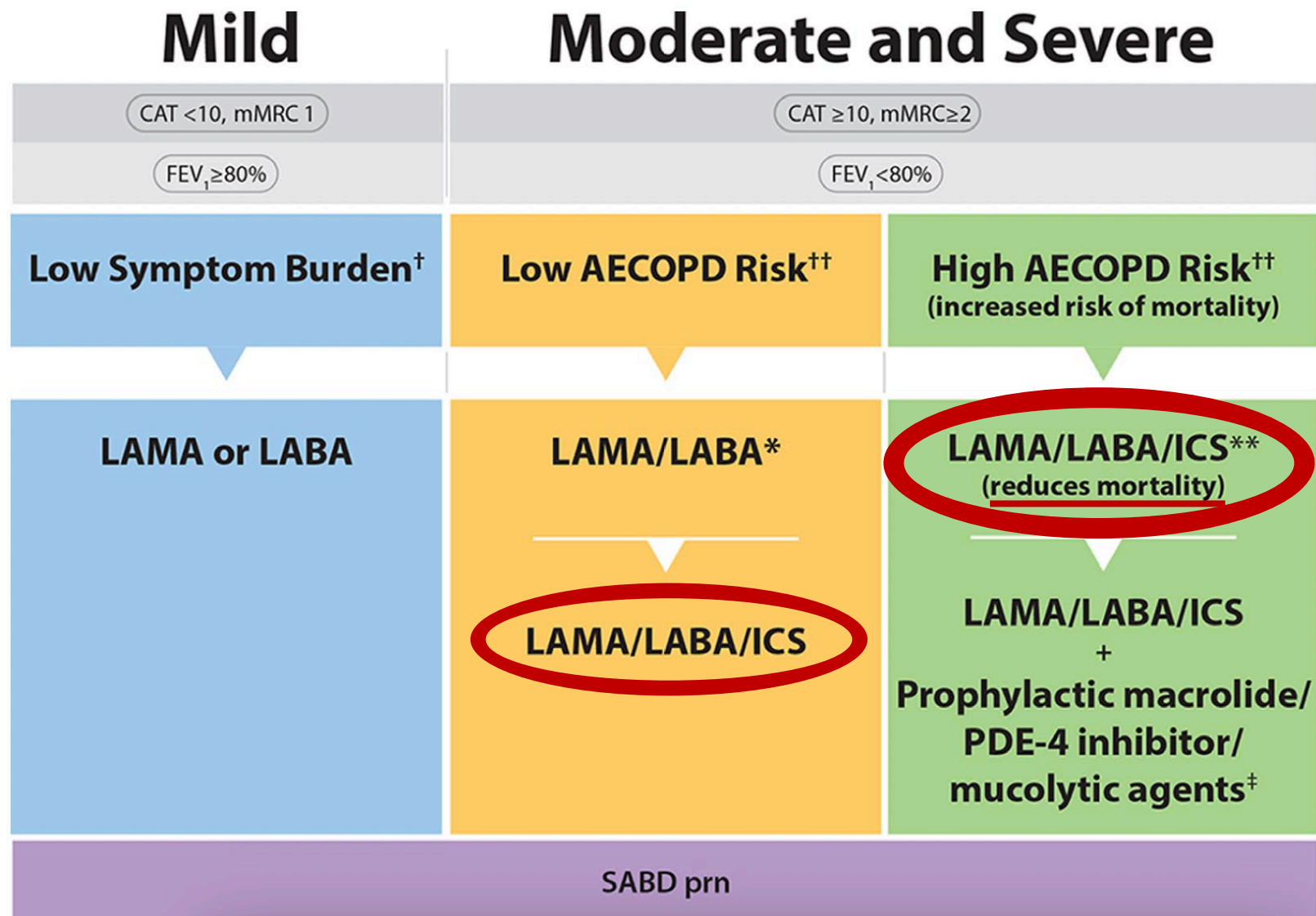
Gillette Introduces New 27 Blade Razor

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



SHOULD WE GO “ALL IN”?

Guidelines say **YES!**



What is the number of moderate/severe AECOPD saved in a year that you'd consider important

(**e.g.** for your patients who have 1-2 AECOPDs/year like Roger)



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



DUAL vs. TRIPLE TRIALS:

OPTIMAL
WISDOM
SUNSET
TRIBUTE
KRONOS

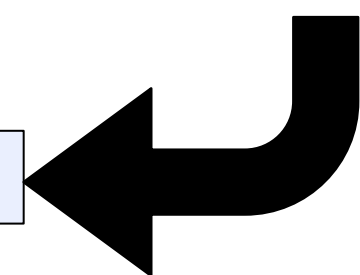
n=6,630

IMPACT
ETHOS

n=12,599

IMPACT *N Engl J Med* 2018;378:1671-80

ETHOS *N Engl J Med* 2020;383:35-48



WHO: FEV1 = ~45%, ≥1 AECOPD/yr (~55% had ≥2)

RESULTS @ 1 yr: → ↓ mod-severe AECOPD = **0.3/patient/yr** (or 1 event saved/3 yrs)
→ ↓ hospitalizations = **no difference (ETHOS)** to 2.3% fewer (IMPACT)
→ ↓ mortality = **~1% less (NNT = 100-120)**

Did patients **FEEL BETTER?** → SGRQ MCID → **NNT = 14**
→ TDI MCID → **NNT = 17**

BENEFIT?

yes, a bit →

What's the
CATCH?

#1

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

#2

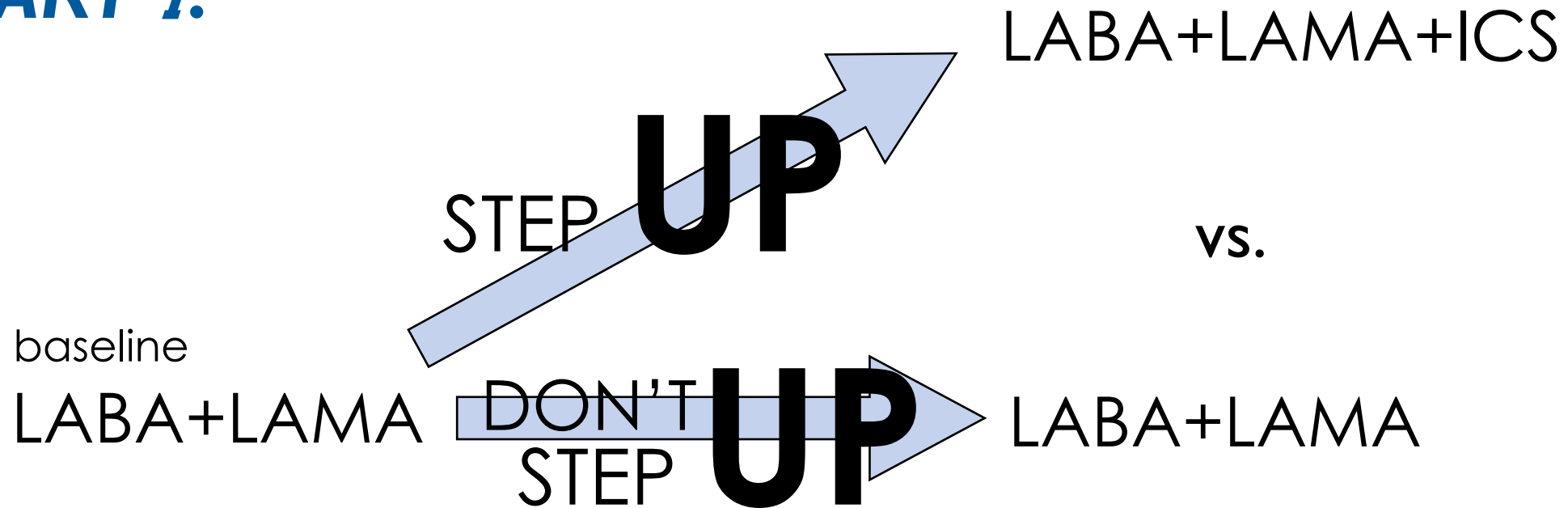
NNH (pneumonia) = 35-60

~40% on triple



HOW **SHOULD** THIS RCT HAVE BEEN DESIGNED? (perspective of a clinician/scientist)

PART 1:



HOW SHOULD THIS RCT HAVE BEEN DESIGNED? (perspective of a clinician/scientist)

PART 2:

Do we want people with asthma in this study?

NO... why?

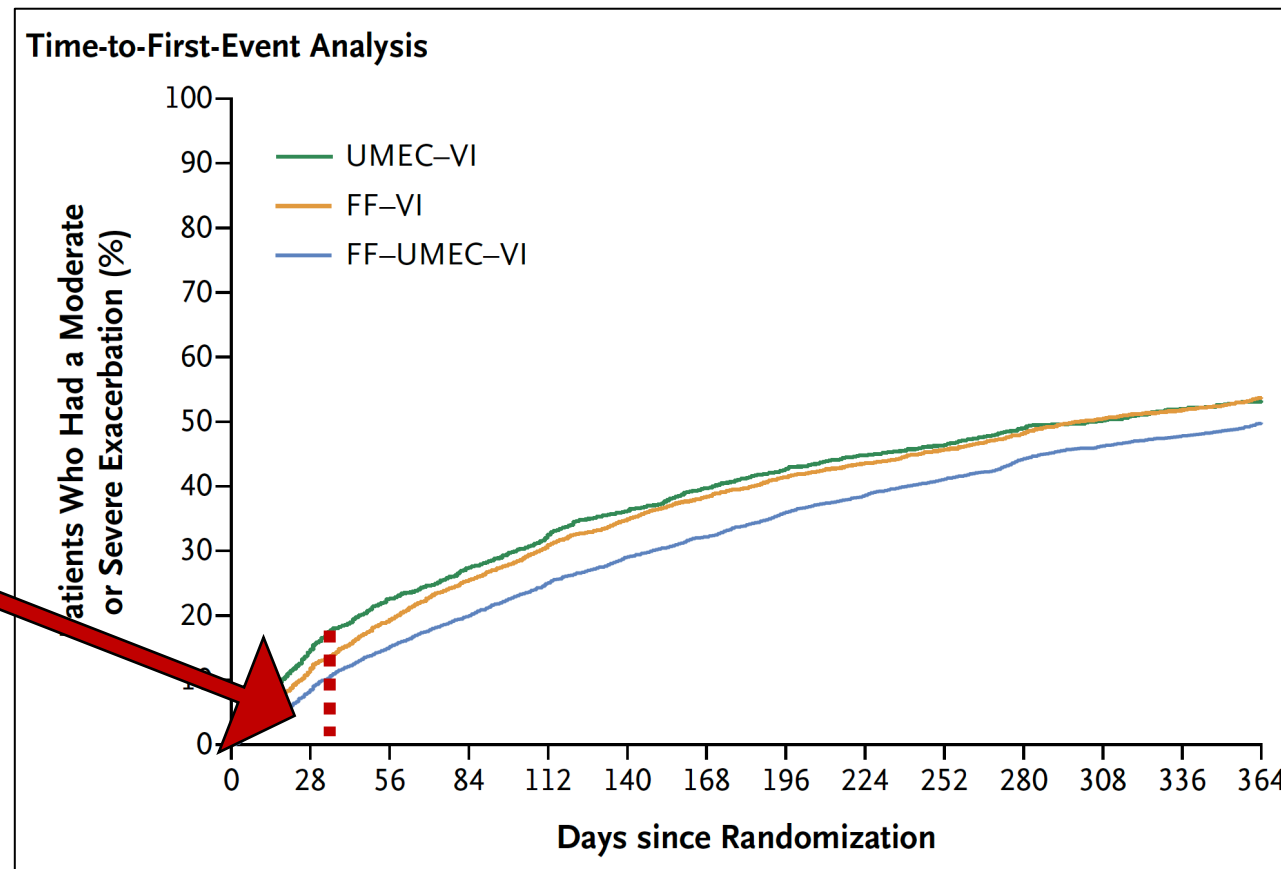
- 1) people with asthma get **++ benefit from ICS** (decreased symptoms, exacerbations, mortality)
- 2) If someone has comorbid asthma AND COPD, I probably want them on ICS anyway → what I want to know is...
- 3) **do people with COPD WITHOUT ASTHMA benefit from ICS?**



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.**”



BEST CASE SCENARIO

(based on a good trial design)

Table 3. Rates of On-Treatment Moderate/Severe Exacerbations in IMPACT by Medication at Study Entry

Baseline Medication*	TRIPLE		DUAL	
	FF/UMEC/VI (95% CI)	FF/VI (95% CI)	UMEC/VI (95% CI)	
Overall	0.91 (0.87–0.95)	1.07 (1.02–1.12)	1.21 (1.14–1.29)	
ICS/LAMA/LABA	0.5 saved 1.21 (1.13–1.28)	1.43 (1.35–1.53)	1.72 (1.58–1.87)	
ICS/LABA	0.70 (0.64–0.77)	0.85 (0.78–0.92)	0.94 (0.83–1.06)	
LAMA/LABA	0.2 saved 0.84 (0.73–0.98)	1.11 (0.95–1.29)	1.05 (0.86–1.29)	
LAMA	0.65 (0.54–0.78)	0.75 (0.64–0.89)	0.61 (0.47–0.80)	

Bad design

0.5 saved

1.21 (1.13–1.28)

1.72 (1.58–1.87)

Good design

0.2 saved

0.84 (0.73–0.98)

1.05 (0.86–1.29)



~1 AECOPD saved every 5 yrs (unlikely to be severe)

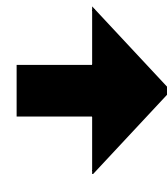
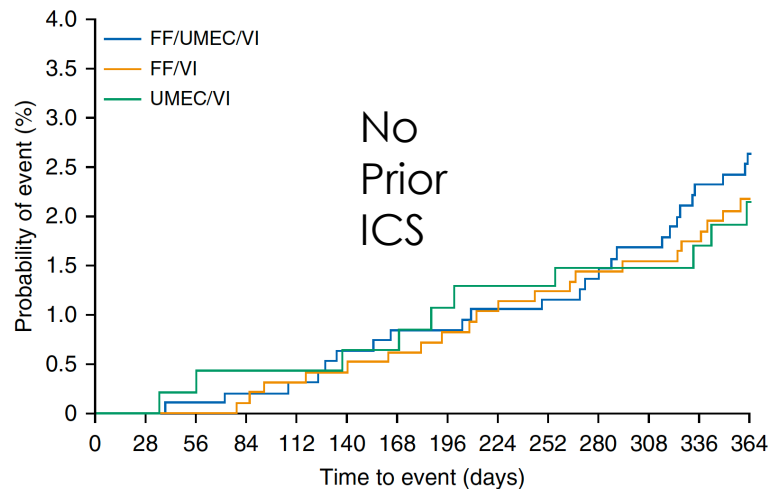
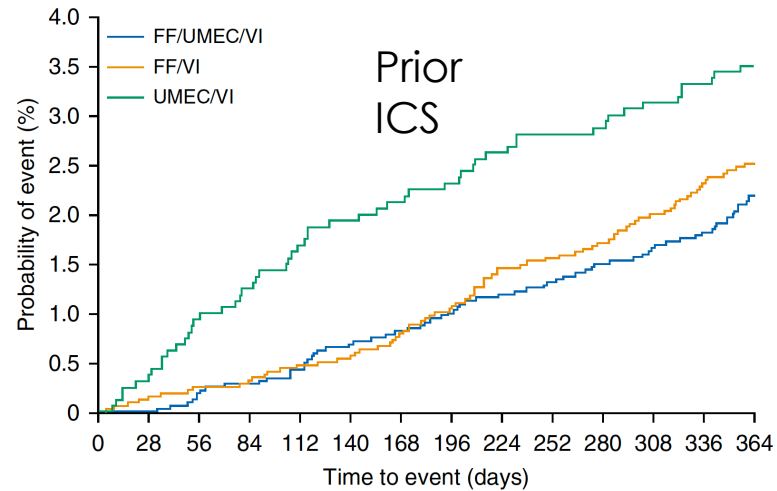
Am J Respir Crit Care Med;101(12):1508–1516, Jun 15, 2020



Effect of ICS use at baseline on... **MORTALITY**

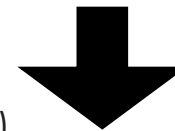
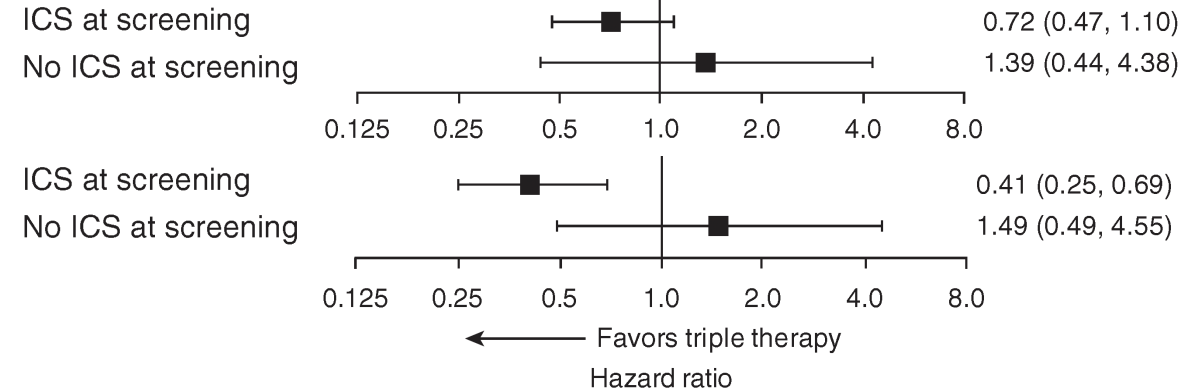
IMPACT

(*Am J Respir Crit Care Med* 2020;101(12):1508–1516)



ETHOS

(*Am J Respir Crit Care Med* 2021 Mar 1;203(5):553-564)



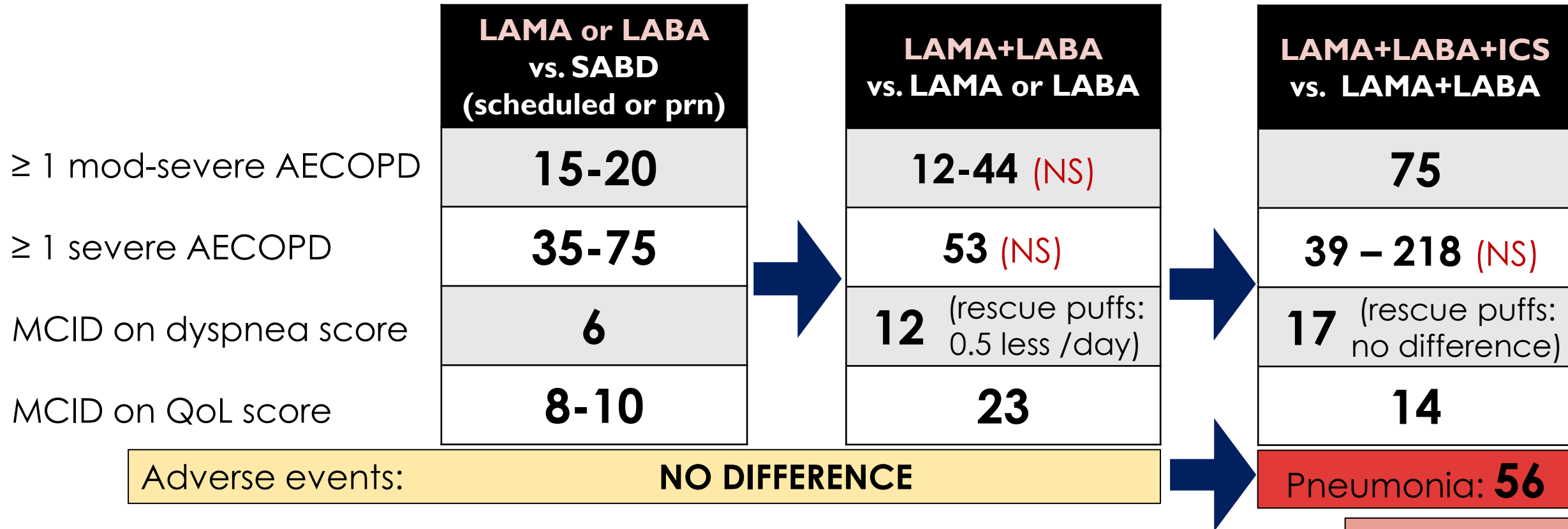
Suissa

(*ERJ Open Res* 2023; 9:00615-2022)



Recall... CTS algorithm for triple therapy states “reduces mortality”

NNTs... diminishing returns (ballpark)



BEST CASE SCENARIO

- Other AEs:
- thrush
 - dysphonia
 - fractures

Thorax 2016;71:15-25 CDSR 2018, Issue 12. Art. No.: CD012620
 Int J COPD 2017;12 907-922 Respir Res 2017;18:196 CDSR 2015, Issue 10. Art. No.: CD008989
 Dalhousie CPD Academic Detailing Service, 2017 Chronic Obstr Pulm Dis 2023;10(1):33-45
 Can J Respir Crit Care Sleep Med 2023;7(4):173-191(Suppl 2) Int J COPD 2022;17 3061-3073

for the most part...

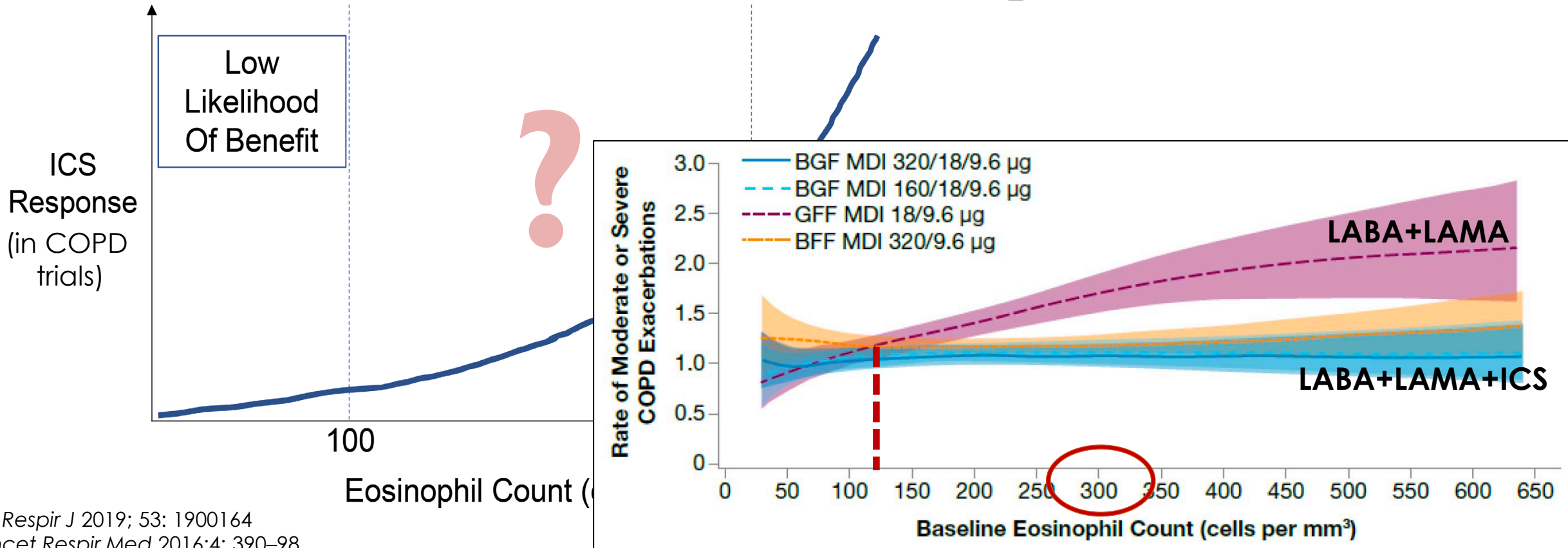
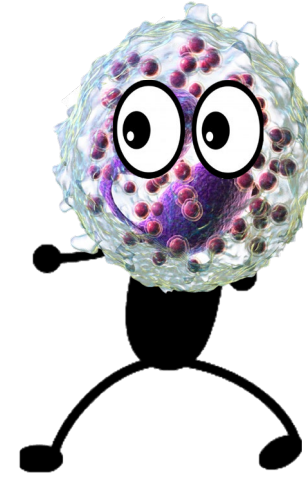
TRELEGY FOR COPD HAS

THE POWER OF 1, 2, 3* = THE POWER OF 1, 2



HEY, EOSINOPHIL...

WHAT CAN YOU TELL US?



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)

HOW MUCH BETTER MIGHT IT BE?



Other factors:

~815km/yr
(Kimberley to Vancouver)



Breztri
(budesonide
glycopyronium
formoterol)



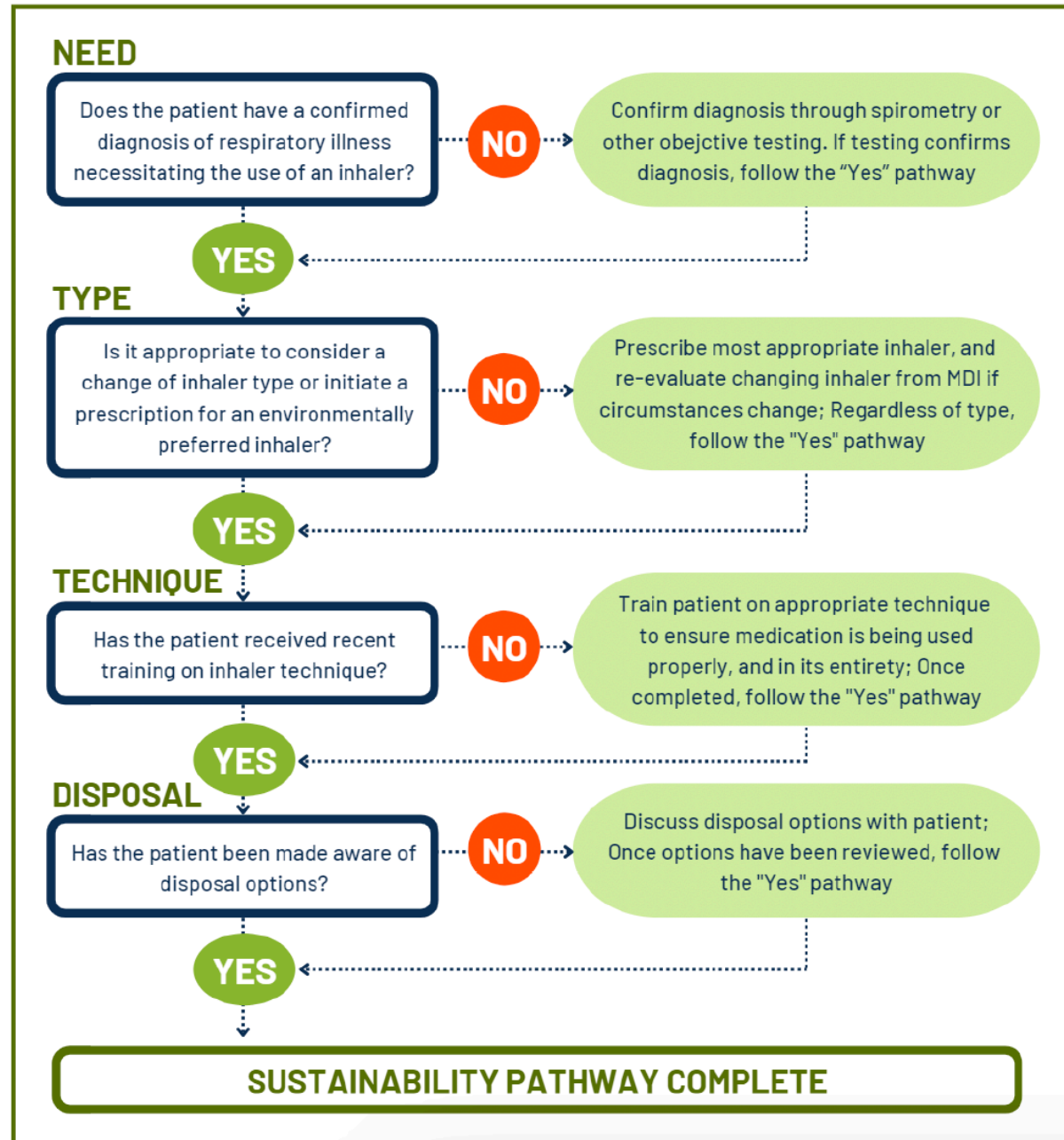
Trelegy
(fluticasone
umeclidinium
vilanterol)

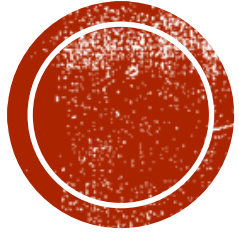


~45km/yr
(Kimberley to Lumberton)

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

WHAT ELSE SHOULD WE DO?





QUESTIONS

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