CTS GUIDELINE

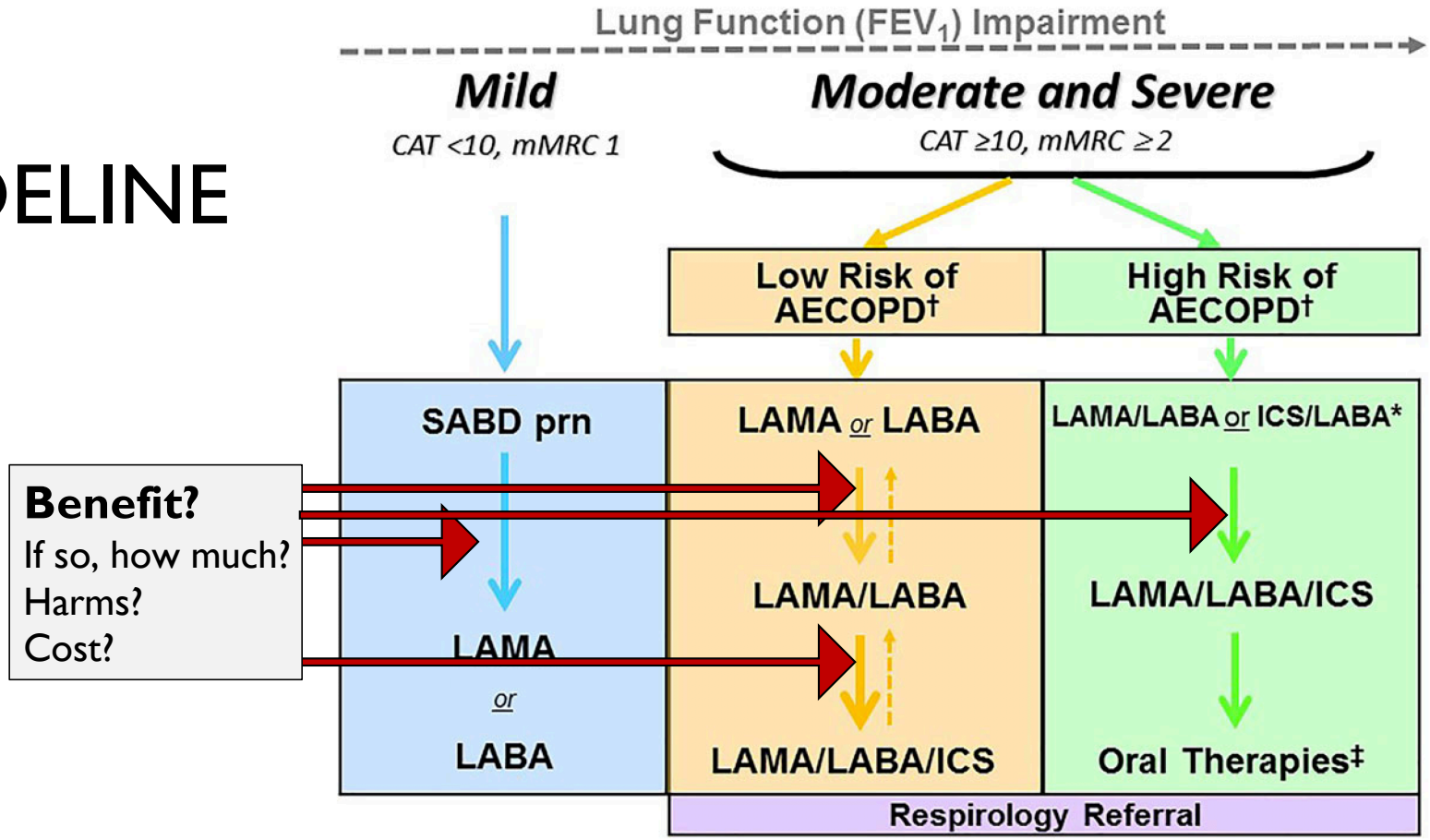
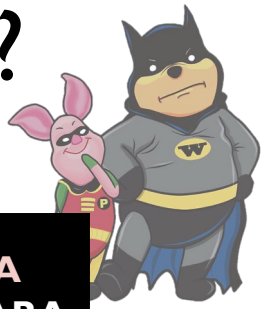


Figure 2. COPD Pharmacotherapy.

Can J Respir Crit Care Sleep Med Oct 2019, DOI: 10.1080/24745332.2019.1668652

NNTs... diminishing returns?
(ballpark)



	LAMA or LABA vs. SABD (scheduled or prn)	LAMA+LABA vs. LAMA or LABA
≥ 1 mod-severe AECOPD	**16-29**	**42**
≥ 1 severe AECOPD	**36**	**NS**
MCID on dyspnea score	**6**	**6-15**
MCID on QoL score	**8-10**	**8-15**
Adverse events:	NO DIFFERENCE	

LAMA+LABA+ICS vs. LAMA+LABA

?

(how well is this collected and reported?)

Thorax 2016;71:15–25 *CDSR* 2018, Issue 12. Art. No.: CD012620
Int J COPD 2017:12 907–922 *Respir Res* 2017;18:196
COPD: What to Do with all These New Inhalers? Dalhousie CPD Academic Detailing Service, 2017

BACK IN TIME…

AECOPD *VS.* PNEUMONIA IN CONTEXT

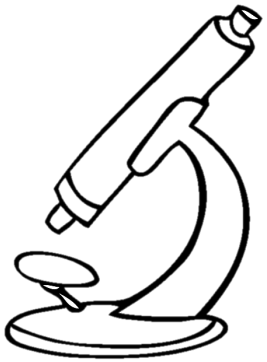


Table 2 Comparison between the NNT to prevent a COPD exacerbation and the NNT to induce pneumonia properly computed from the corresponding cumulative incidences (CIs) for recent trials of the fluticasone-salmeterol combination inhaler (ICS) versus a long-acting bronchodilator

		COPD exacerbation			Pneumonia		
		CI at end of study			CI at end of study		
Study	Time span for NNT	ICS	No ICS	NNT	ICS	No ICS	NNT
TORCH[1]	3 years	0.922*	0.945*	44	0.196	0.133	16
INSPIRE[4]	2 years	0.578†	0.590†	83	0.094	0.049	22
Kardos[3]	44 weeks	0.47	0.55	13	0.045	0.014	32
Ferguson[5]	1 year	0.58	0.66	13	0.07	0.04	33
Anzueto[6]	1 year	0.60	0.67	14	0.07	0.02	20

n=6112

n=7435

n=2573

Suissa S. Thorax 2013;68:540–543.

LABA+ICS GOES DOWN IN **FLAME**S?

ORIGINAL ARTICLE

Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD

X 1 yr

N Engl J Med 2016;374:2222-34

- Patients (n=3362)
  - At least one moderate exacerbation in the past year
  - **75%** were GOLD stage D (i.e. **severe**)

- **Results:**
  - **0.21** less exacerbations/pt/yr for LAMA+LABA
  - 1.8 point difference in QoL (SGRQ)
  - ¼ puff less/day of rescue inhaler
  - Pneumonia: **NNH = 63** for LABA+ICS

So, **LAMA+LABA modestly better** than **LABA+ICS** in the highest risk patient, **and safer**

NOTABLE **TRIPLE** TRIALS:

N=12,851

- OPTIMAL
- WISDOM
- SUNSET
- TRIBUTE
- KRONOS

n=6,630

- IMPACT → n= 6,221

N Engl J Med 2018;378:1671-80

Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD

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

WHAT? LABA+LAMA+ICS (fluticasone) vs. LABA+LAMA vs. ICS+LABA

What did they find @ 1yr?

→ ⬇ mod-severe AECOPD = **0.3/pt/yr**

→ ⬇ hospitalizations **= 0.06/pt/yr**

→ ⬇ mortality = **0.83%, NNT=120**

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

→ SQRQ **-1.8** → **NNT MCID = 13**

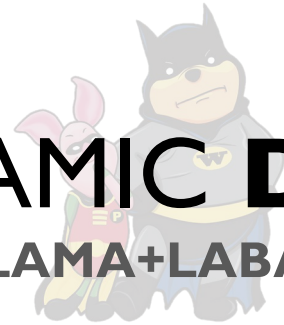
→ TDI change **not reported** → **MCID NNT = 17?**

IMPACT? → yes, a bit →

What's the CATCH?

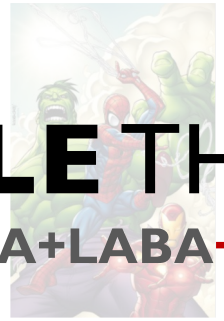
#1
- you could have history of **ASTHMA**
- **>70% on ICS** pre-randomization

#2 **NNH (pneumonia) = 34**



DYNAMIC **DUO** *vs.* **TRIPLE** THREAT

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



3 meta-analyses:

- Reduction in **AECOPD** (Cazzola, *Eur Resp J* 2018)

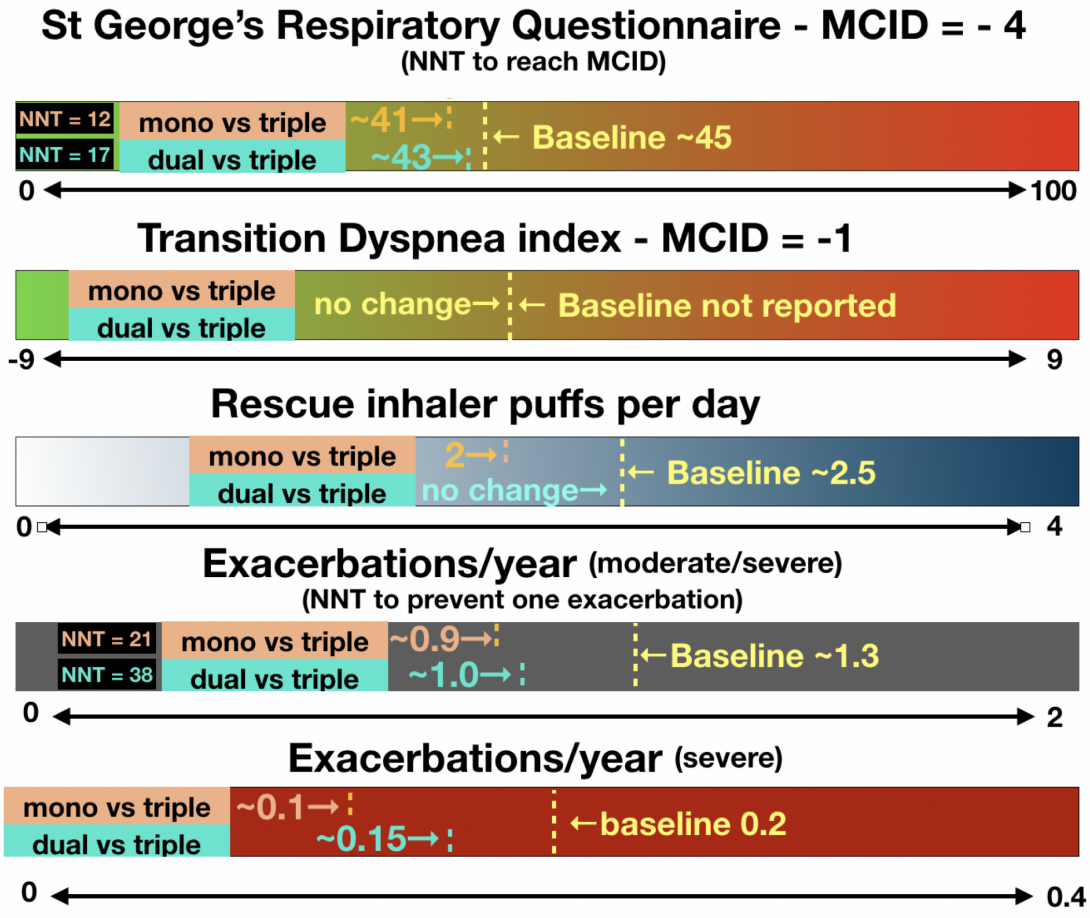
  NNT = **39** (for triple)

- 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?

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



NNTs... diminishing returns?
(ballpark)

any real net benefit?

	LAMA or LABA vs. SABD (scheduled or prn)	LAMA+LABA vs. LAMA or LABA	LAMA+LABA+ICS vs. LAMA+LABA
≥ 1 mod-severe AECOPD	**16-29**	**42**	**38**
≥ 1 severe AECOPD	**36**	**NS**	**0.05 less/pt/yr**
MCID on dyspnea score	**6**	**6-15**	**NA**
MCID on QoL score	**8-10**	**8-15**	**17**
Adverse events:	NO DIFFERENCE		Pneumonia: **39**

Thorax 2016;71:15–25 *CDSR* 2018, Issue 12. Art. No.: CD012620
Int J COPD 2017:12 907–922 *Respir Res* 2017;18:196
COPD: What to Do with all These New Inhalers? Dalhousie CPD Academic Detailing Service, 2017

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%, ≥1 AECOPD/yr (57% had ≥2)

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

What did they find @ 1yr?

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

→ ⬇ hospitalizations **= NS**

* → ⬇ mortality = **1.0% NNT=100** (320mcg), 0.47% (NNT=212) (160mcg)

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

→ SQRQ change **-1.9 (320mcg)**, **-1.5 (160mcg)** → **NNT MCID = 13-15**

→ TDI change 0.4 (both doses) @24 wks → **MCID NNT not reported**

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

IMPACT:
EFFECT OF ICS USE AT BASELINE ON AECOPD

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

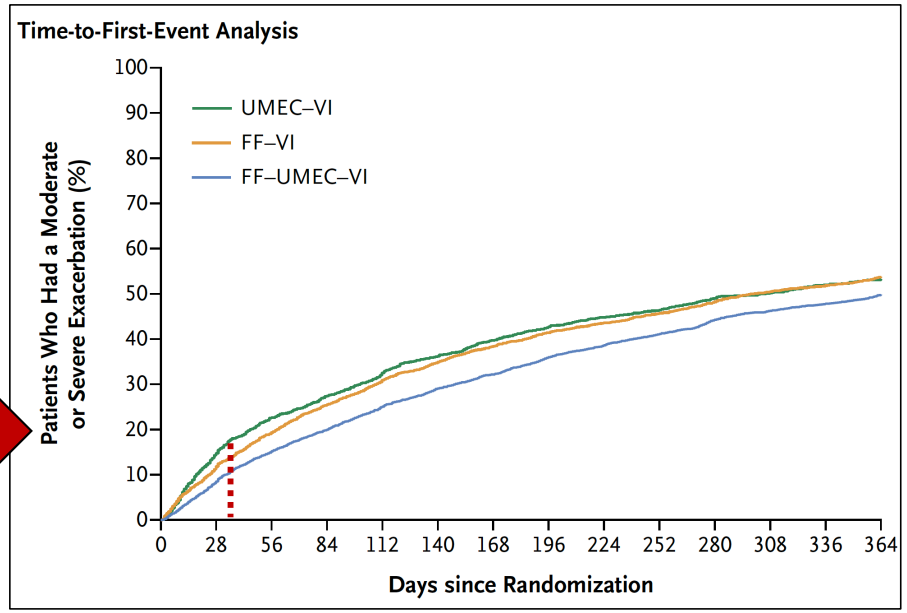
Table 3. Rates of On-Treatment Moderate/Severe Exacerbations in IMPACT by Medication at Study Entry

Baseline Medication*	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	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	0.84 (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)

"…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."

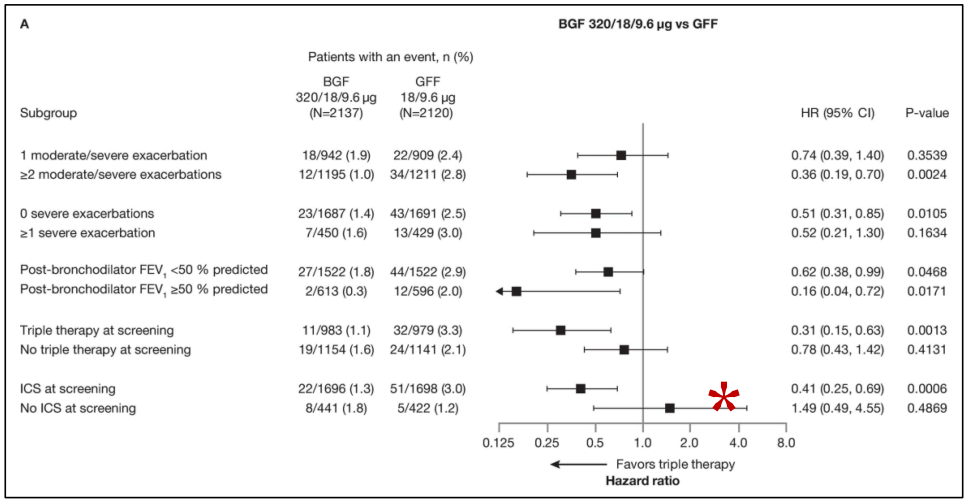
Suissa, Drazen, *NEJM* April 18, 2018 NEJM

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



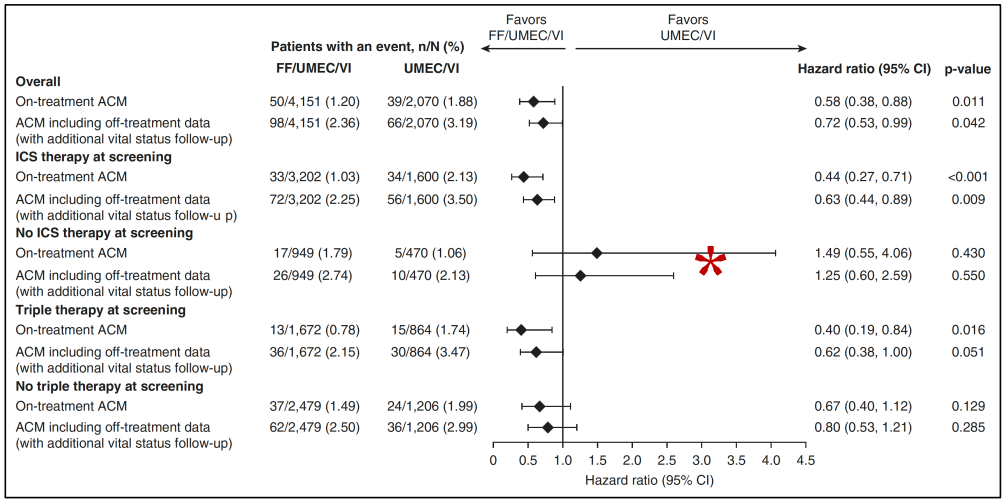
ETHOS & IMPACT:
EFFECT OF ICS USE AT BASELINE ON MORTALITY

ETHOS



AJRCCM Articles in Press. Published November 30, 2020 as 10.1164/rccm.202006-2618OC

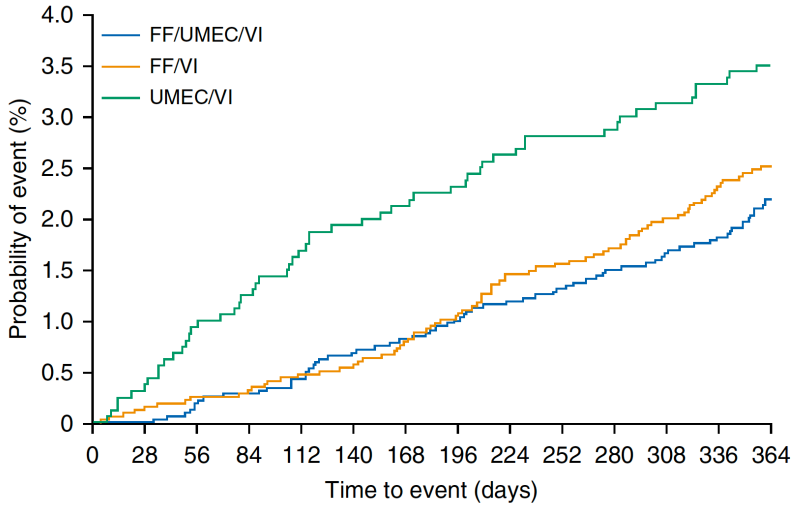
IMPACT



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

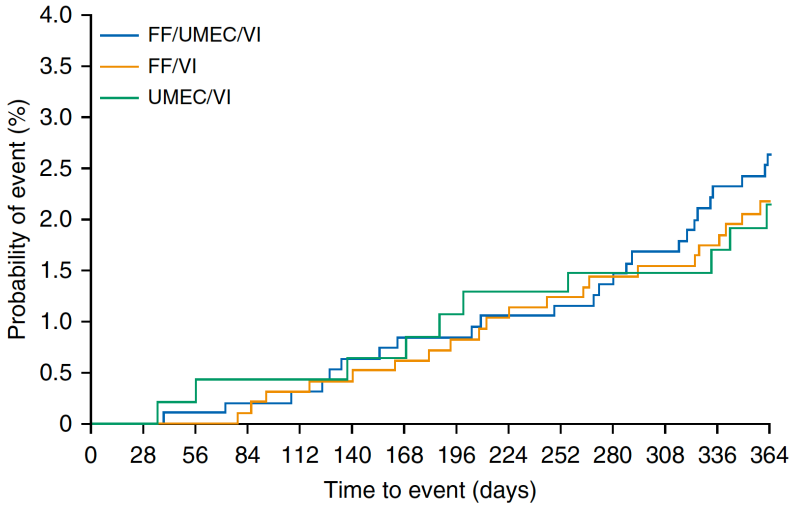
IMPACT:
EFFECT OF ICS USE AT BASELINE ON MORTALITY

ICS at screening



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

No ICS at screening



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

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

PRIMARY CARE *vs.* TRIALS

https://www.trelegy.com

Plos One 2014;9(3):e90145

Table 2. Baseline comparison of the UNLOCK studies versus large COPD studies, including independent sample t-tests.

Characteristic	(primary care) UNLOCK studies	Large COPD studies (LPCS)	Mean difference between UNLOCK – LPCS (95% CI)	p-value
Patients (N)	3508	23860		
Age, years	66.1 (2.3)	63.7 (0.9)	−2.4 (−4.6 — −0.3)	0.03*
Male, %	60.9 (16.7)	73.3 (4.1)	12.4 (−3.1—27.9)	0.1
Current smokers, %	42.9 (9.5)	40.7 (8.6)	−2.2 (−13.2—8.8)	0.67
Pack years	43.6 (13.5)	44.9 (4.03)	1.3 (−15.2—17.8)	0.84
BMI, kg/m^2	26.3 (0.5)	25.6 (0.9)	−0.7 (−2 —0.6)	0.23
Postbronchodilator FEV$_1$, % predicted	63.8 (8.7)	47.4 (2.4)	−16.4 (−24—−8.2)	<0.01*
FEV1:FVC, %	55.7 (0.7)	46.5 (4.0)	−9.2 (−14.1 —−4.2)	<0.01*
GOLD distribution				
Mild GOLD I	20.7 (13.2)	-	-	-
Moderate GOLD II	53.3 (6.2)	45 (6.3)	−8.3 (−16.6—0.1)	0.05
Severe GOLD III	21 (10.1)	44.5 (3.1)	23.5 (13.9—33.1)	<0.01*
Very severe GOLD IV	5.8 (5.2)	11.5 (3.5)	5.7 (−0.71—12)	0.08
Patient-reported outcomes				
SGRQ	32.6 (6.2)	48.4 (1.9)	15.8 (6.3—25.4)	0.01*
CCQ (mean)	1.6 (0.3)	-	-	-
MRC (mean)	2.1 (0.8)	2.7 (1.1)	0.6 (−1.5—2.7)	0.5
MRC score > 2 (%)	32.3 (17)	51.5 (2.1)	19.2 (1.3—37)	0.04*

Better FEV1

Less GOLD

Better QoL

* proportion of primary care patients eligible for inclusion in large RCTs → **17% - 42%**

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

i.e. HOPE patient is one of the few that gets ☐ AECOPD

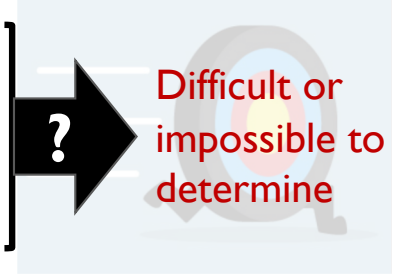
2) SYMPTOM-based

→ prescribe the inhaler → assess if patient feels better

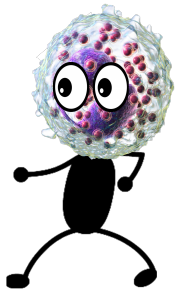
Problems…

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

? Difficult or impossible to determine

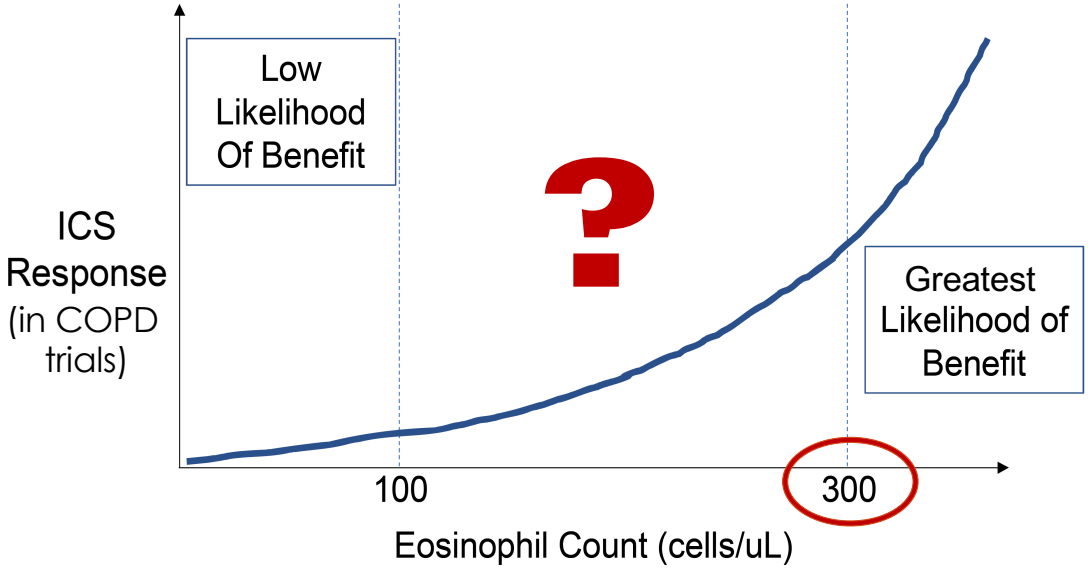


HEY, **EOSINOPHILS…**
WHAT CAN YOU TELL US?



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

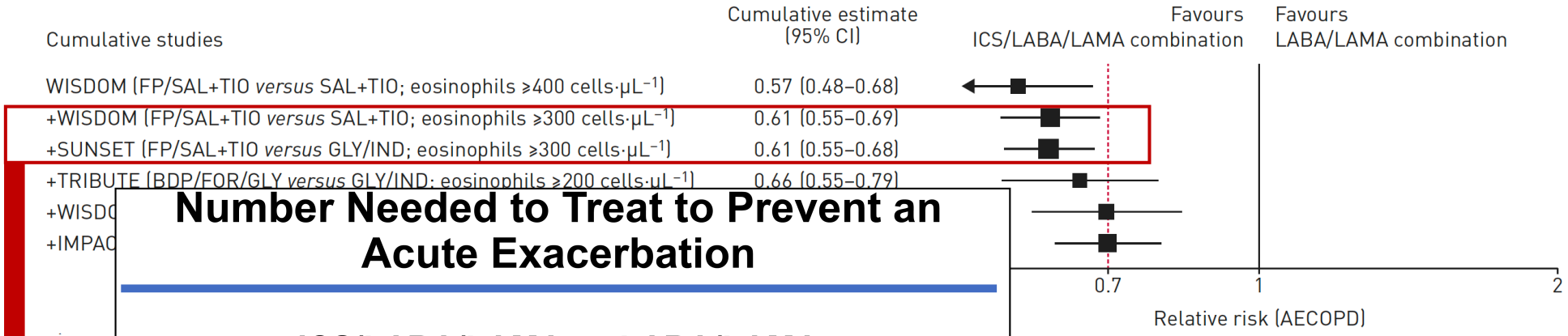
- **Airway eosinophilia** is a hallmark inflammatory response in asthma and is involved in the **airway inflammatory process** in COPD
- **Blood eosinophil counts might reflect degree of sputum eosinophilia** which is increased in some patients with AECOPD



Eur Respir J 2019; 53: 1900164
Lancet Respir Med 2016;4: 390–98
Int J COPD 2018:13 2775–2784

BACK TO THE META-ANALYSIS…

a **TRIBUTE** to the **IMPACT** of **SUNSETS** on **WISDOM**



Cazzola, *Eur Respir J* 2018

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)

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

Lancet Respir Med 2019;7: 745–56

APPLICATION

(caveat: ideally, this would be tested in an RCT)

Is it reasonable to consider a level ?

- **IF…**
  - patient already on LAMA+LABA, **AND**
  - continues to be symptomatic **+** history of AECOPD

Then…

- **IF** the level is "high" (>300)… what do we do?

→ ***adequately inform patient of:***

1. estimated chance of benefit
2. uncertainty of dyspnea, QoL improvement
3. estimated risk of pneumonia
4. cost/month (MB): $140 (triple) *vs.* $65 (dual)

→ What do **THEY** want to do?

Triple therapy trials in COPD: a precision medicine opportunity

Samy Suissa[1] and Amnon Ariel[2]

Eur Respir J 2018; 52: 1801848

With reference to future study populations:

*"…pre-specified stratification of the results by **important effect-modifiers, such as prior asthma, airflow limitation, exacerbation frequency and the degree of eosinophilia**, could provide a precision medicine approach to COPD management. Such a modern approach will permit the identification of **subsets of patients who could benefit from triple therapy and avoid harms in a number of patients for whom triple therapy is not more effective than dual bronchodilators."***

To be continued?