보건의료전문가용

The Real World Evidence of Single Inhaler Triple Therapy in COPD

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PM-KR-FVU-PPTX-230005 Mar 2023

DISCLAIMER

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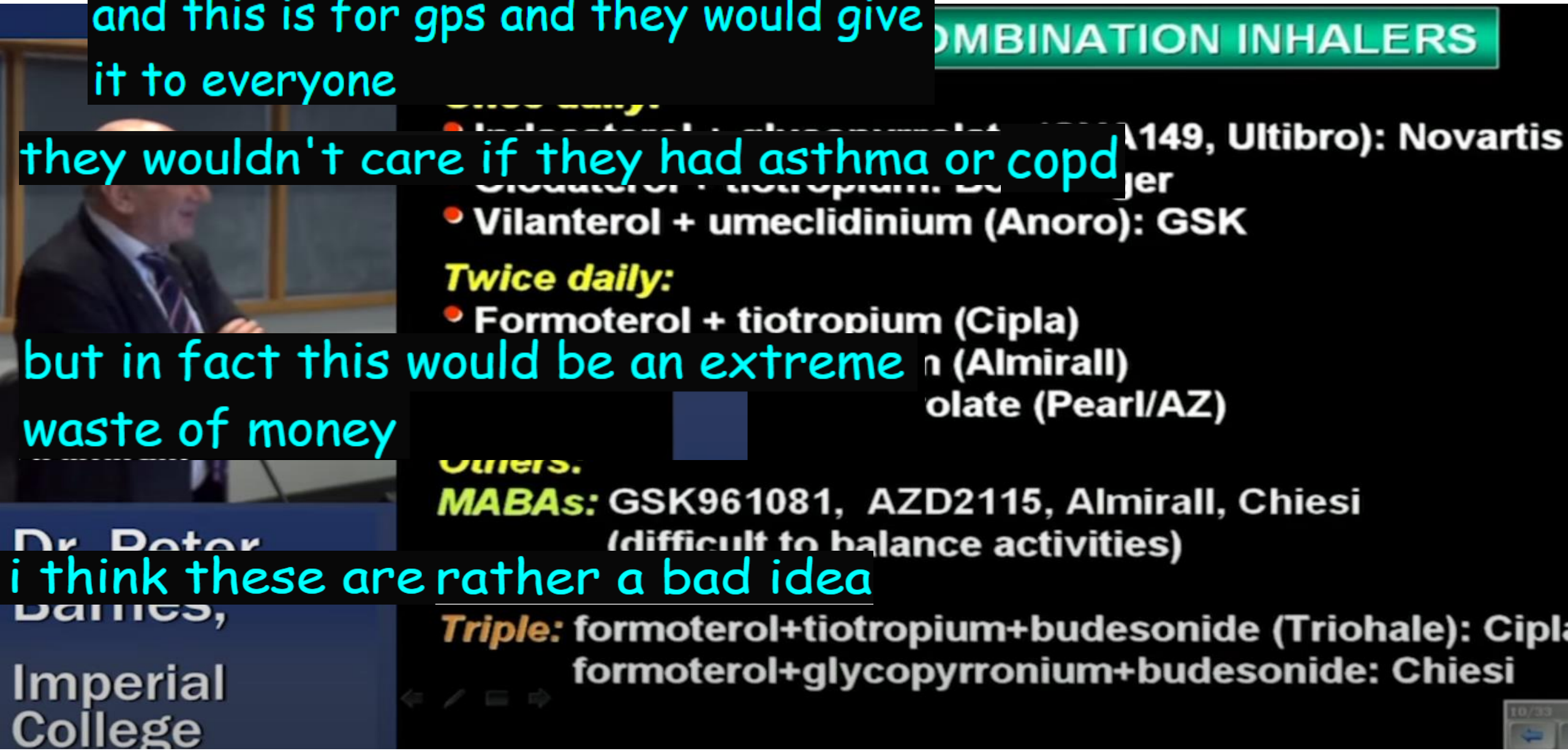
(This event is organized and fully funded by GSK and contains promotional information.)

Dr. Peter Barnes: " Current and Future Treatment of COPD “

2013 Gairdner symposium at St. Paul's Hospital, Vancouver, B.C.



Why the need for *Triple* therapy in COPD?

84%

Patients have high **symptom burden** (CAT>10) despite any LABA/ICS therapy

25-50%

Patients have COPD **exacerbations** despite any LABA/ICS therapy

23-50%

Patients have COPD **exacerbations** despite any LABA/LAMA therapy

npj Primary Care Respiratory Medicine (2020) 30:1
NEJM 2020: 383: 35-48
ERJ 2014: 44: 1548-1556
Respiratory Medicine 2012;106:257-268
Respiratory Medicine 2017;26:105-115

Contents

- The evidence of single inhaler triple therapy in RCT study
- Real world evidence of single inhaler triple therapy
- The issue of Device

Contents

Lung Function, and Health-Related Quality of Life Outcomes in the TRILOGY, KRONOS, FULFIL

Triple therapy clinical trials

2016

2017

2018

	Primary Endpoint: FEV_1 and/or SGRQ			
	TRILOGY[25]	KRONOS[20]	FULFIL[21,87]	
	52 Weeks	24 Weeks	24 Weeks	52 Weeks
		Triple vs LABA/LAMA vs ICS/LABA		
Study arms	BDP/FM/GLY BID (N=687) BDP/FM BID (N=680) Triple vs ICS/LABA	1. BUD/GLY/FM BID (N=639) 2. FM/GLY BID (N=625) 3. BUD/FM BID (N=314) 4. BUD/FM DPI open-label BID (N=318)	FF/UMEC/VI QD (N=911) BUD/FM BID (N=899) Triple vs ICS/LABA	FF/UMEC/VI QD (N=210) BUD/FM BID (N=220)
Pre-dose FEV_1 (mean change from baseline, mL)	71 vs 8 Mean difference: 63, 95% CI: 32, 94, P<0.001	147 vs 125 vs 73 vs 88 Mean difference (1 vs 2): 22, 95% CI: 4, 39, P=0.014 Mean difference (1 vs 3): 74, 95% CI: 52, 95, P<0.0001 Mean difference (1 vs 4): 59, 95% CI: 38, 80, P<0.0001[a]	142 vs −29 Mean difference: 171, 95% CI: 148, 194, P<0.001	126 vs −53 Mean difference: 179, 95% CI: 131, 226, P<0.001
SGRQ total score (mean change from baseline)	Mean difference: −1.69, 95% CI: −3.20, −0.17, P=0.029	−7.5 vs −6.3 vs −7.1 vs −6.3 Mean difference (1 vs 2): −1.22, 95% CI: −2.30, −0.15, P=0.0259[b] Mean difference (1 vs 3): −0.45, 95% CI: −1.78, 0.87, P=0.5036 Mean difference (1 vs 4): −1.26, 95% CI: −2.58, 0.06, P=0.0617	−6.6 vs −4.3 Mean difference: -2.2, 95% CI: −3.5, −1.0, P<0.001	−4.6 vs −1.9 Mean difference: −2.7, 95% CI: −5.5, 0.2, P=0.065

International Journal of Chronic Obstructive Pulmonary Disease 2021:16 499–517

Moderate/severe exacerbation rate, per year **exacerbation**	0.41 vs 0.53 Rate ratio: 0.77, 95% CI: 0.65, 0.92, P=0.005	0.46 vs 0.95 vs 0.56 vs 0.55 Rate ratio (1 vs 2): 0.48, 95% CI: 0.37, 0.64, P<0.0001 Rate ratio (1 vs 3): 0.82, 95% CI: 0.58, 1.17, P=0.2792 Rate ratio (1 vs 4): 0.83, 95% CI: 0.59, 1.18, P=0.3120	0.22 vs 0.34 Rate ratio: 0.65, 96% CI: 0.49, 0.86, P=0.002	0.20 vs 0.36 Rate ratio: 0.56, 95% CI: 0.37, 0.85, P=0.006
	Primary Endpoint: FEV_1 and/or SGRQ			
	TRILOGY[25]	**KRONOS[20]**	**FULFIL[21,87]**	

Triple vs ICS/LABA

Triple vs LABA/LAMA vs ICS/LABA

Triple vs ICS/LABA

International Journal of Chronic Obstructive Pulmonary Disease
2021:16 499–517

Triple therapy clinical trials

Exacerbation Rate in the TRIBUTE, ETHOS, and IMPACT Trials

2018

2018

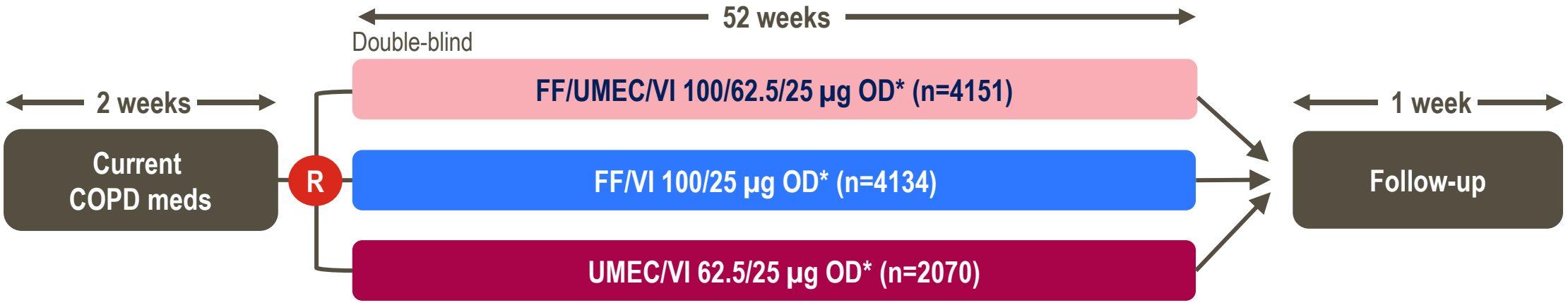
	Primary Endpoint: Exacerbation Rate		
	TRIBUTE[23]	ETHOS[24,88]	IMPACT[22,89]
	52 Weeks	52 Weeks	52 Weeks
Study arms	BDP/FM/GLY BID (N=764) IND/GLY QD (N=768) Triple vs LABA/LAMA	1. BUD (320)/GLY/FM BID (N=2137) 2. BUD (160)/GLY/FM BID (N=2121) 3. FM/GLY BID (N=2120) 4. BUD/FM BID (N=2131) Triple vs LABA/LAMA vs ICS/LABA	1. FF/UMEC/VI QD (N=4151) 2. FF/VI QD (N=4134) 3. UMEC/VI QD (N=2070) Triple vs ICS/LABA vs LABA/LAMA
Recruitment criteria (FEV_1% predicted, exacerbations, and CAT score)	• FEV_1 <50% • ≥1 moderate/severe exacerbation in the preceding year • CAT ≥10	• FEV_1 ≥25–≤65% • ≥1 moderate/severe (if FEV_1 <50%), or ≥2 moderate or ≥1 severe (if FEV_1 ≥50%) exacerbation in the preceding year • CAT ≥10	• FEV_1 <50% plus ≥1 moderate or severe exacerbation in the preceding year; or • FEV_1 ≥50–<80% plus ≥2 moderate or ≥1 severe exacerbation in the preceding year • CAT ≥10
Results (ITT population)			
Moderate/severe exacerbation rate, per year	0.50 vs 0.59 Rate ratio: 0.848, 95% CI: 0.723, 0.995, P=0.043	1.08 vs 1.07 vs 1.42 vs 1.24 Rate ratio (1 vs 2): 1.00, 95% CI: 0.91, 1.10 (P-value not reported) Rate ratio (1 vs 3): 0.76, 95% CI: 0.69, 0.83, P<0.001 Rate ratio (1 vs 4): 0.87, 95% CI: 0.79, 0.95, P=0.003	0.91 vs 1.07 vs 1.21 Rate ratio (1 vs 2): 0.85, 95% CI: 0.80, 0.90, P<0.001 Rate ratio (1 vs 3): 0.75, 95% CI: 0.70, 0.81, P<0.001

2020

International Journal of Chronic Obstructive Pulmonary Disease 2021:16 499–517

ESTABLISHED IN 1812 MAY 3, 2018 VOL. 378 NO. 18

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



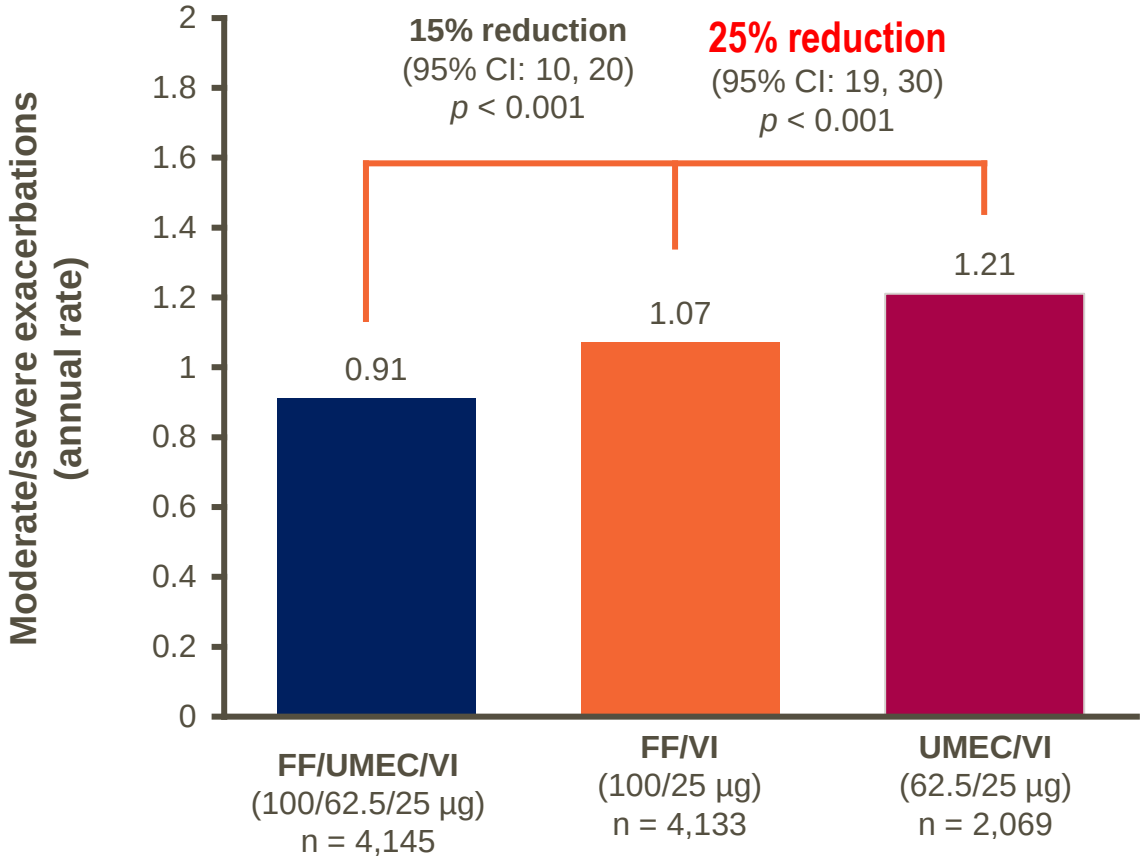
Co-primary treatment comparisons (ITT population)

- Annual rate of moderate/severe exacerbations comparing:
  - FF/UMEC/VI with FF/VI
  - FF/UMEC/VI with UMEC/VI

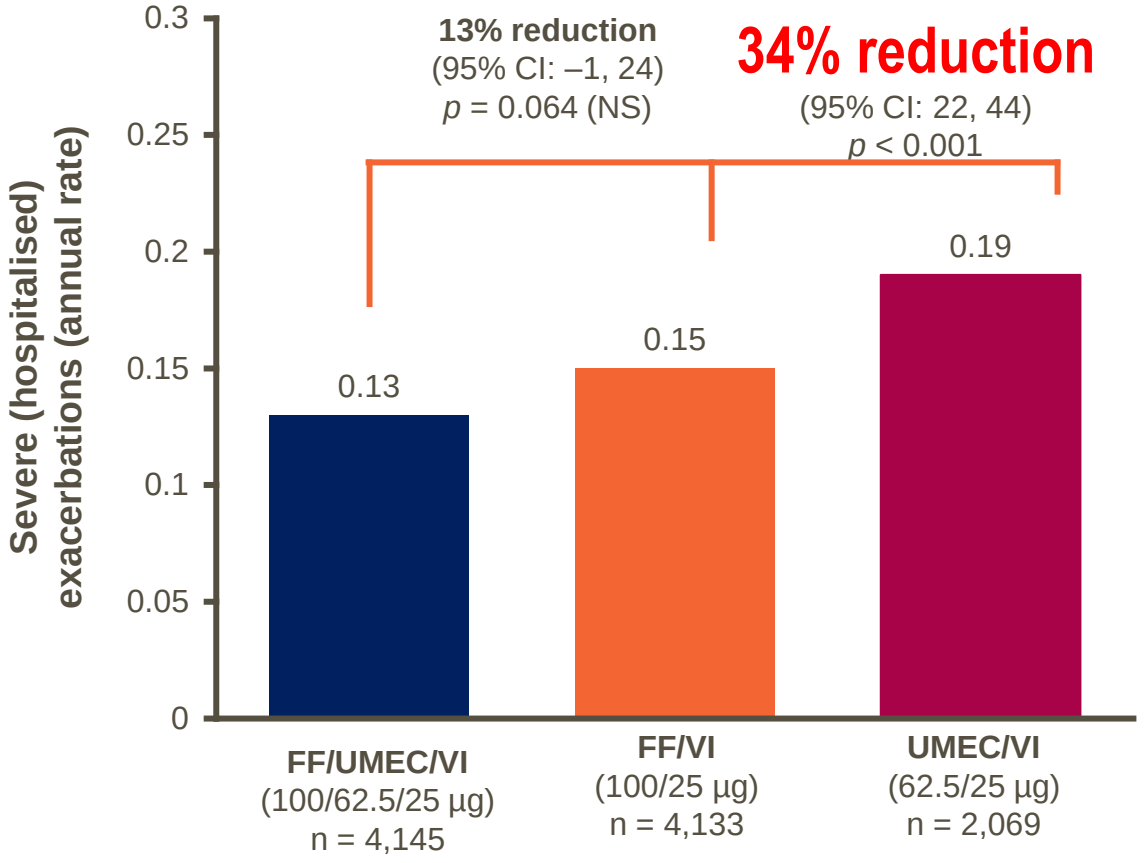
Lipson DA, et al. *N Engl J Med*. 2018

IMPACT: Significant reduction in moderate/severe exacerbations, & reduction in severe (hospitalised) exacerbations with FF/UMEC/VI vs FF/VI & UMEC/VI

Moderate/severe exacerbations



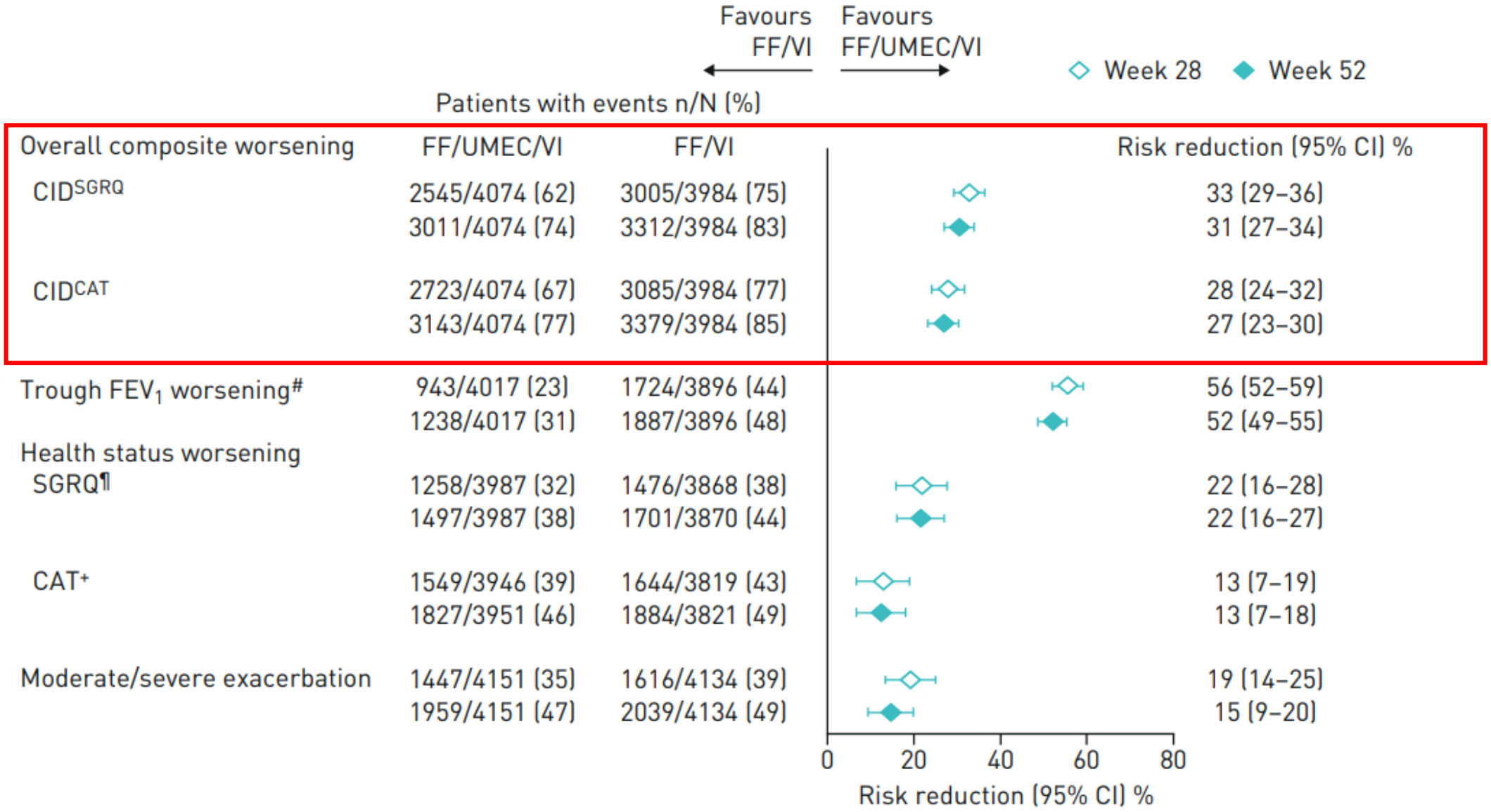
Severe (hospitalised) exacerbations



– FF, fluticasone furoate; NS, not statistically significant; UMEC, umeclidinium; VI, vilanterol.

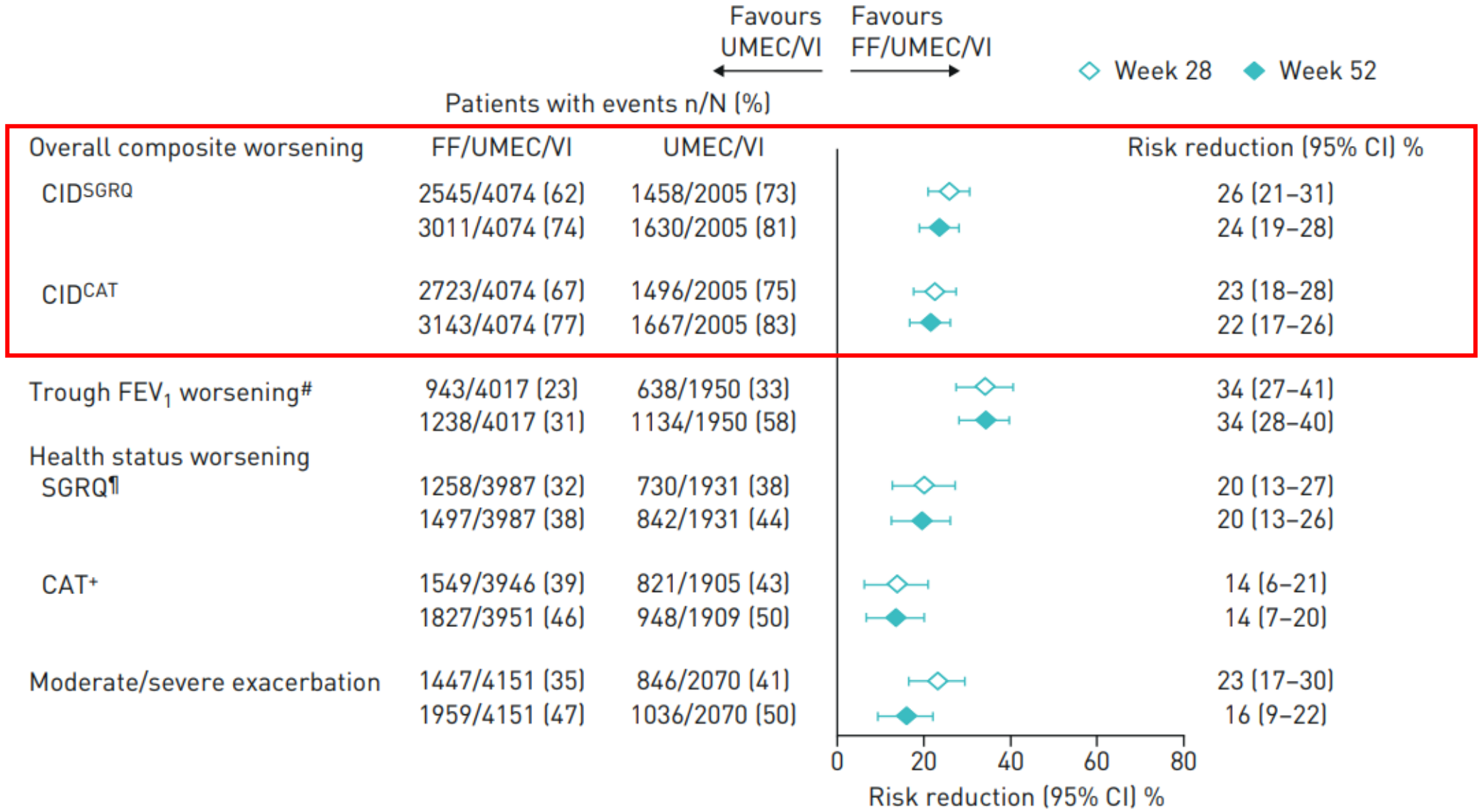
Lipson DA, et al. *N Engl J Med*. 2018;378:1671–1680

Reduction in clinically important deterioration (CID) risk (time to first) with fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) versus FF/VI



Han MK, et al ERJ open research ;2021;7;00663-2020

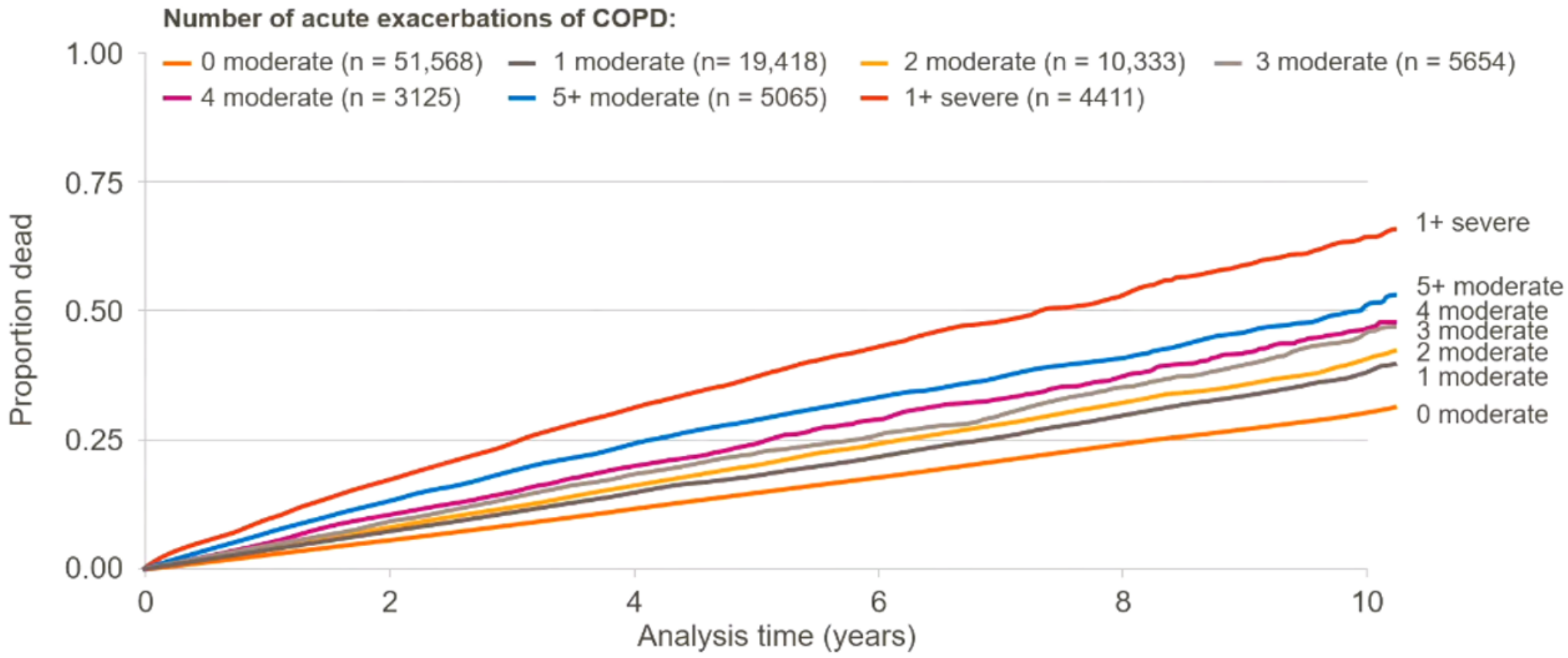
Reduction in clinically important deterioration (CID) risk (time to first) with fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) versus UMEC/VI



Han MK, et al ERJ open research ;2021;7;00663-2020

Proportion of deaths increases with increasing frequency and severity of exacerbations

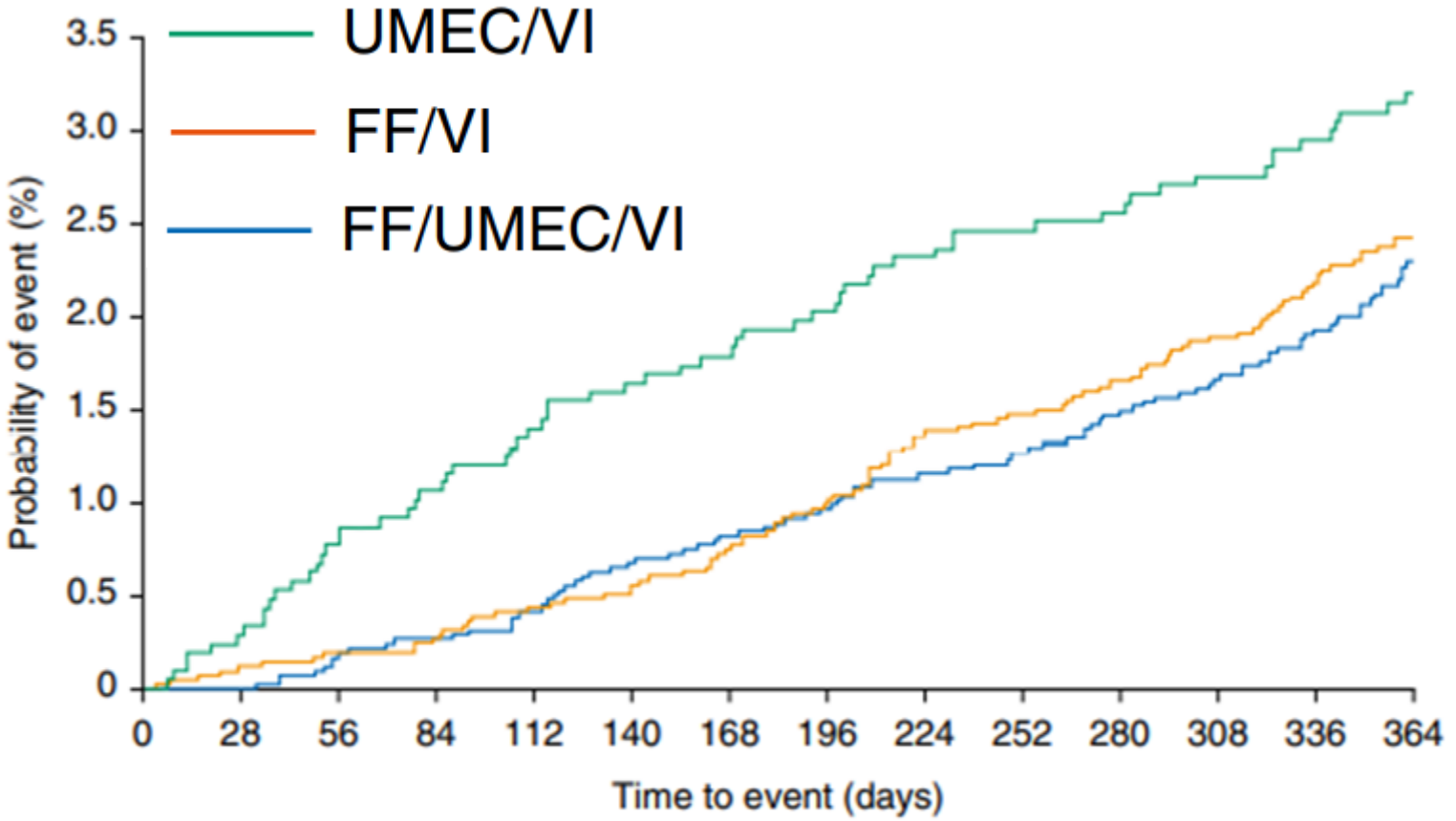
Patients most at risk of dying are those with ≥1 severe exacerbation



Population-based study of 99,574 patients with COPD from the UK Clinical Practice Research Datalink, 1 January 2004–31 March 2015.
Time to death assessed using a Cox proportional hazards model.
COPD, chronic obstructive pulmonary disease.

Adapted from Rothnie KJ, et al. Am J Resp Crit Care Med. 2018;198:464–471.

All-cause mortality (on/off-treatment deaths)



FF/UMEC/VI	4,151	4,150	4,142	4,137	4,131	4,119	4,113	4,107	4,097	4,092	4,082	4,073	4,062	3,919
FF/VI	4,134	4,129	4,123	4,118	4,111	4,106	4,095	4,082	4,065	4,060	4,050	4,040	4,027	3,848
UMEC/VI	2,070	2,063	2,052	2,045	2,037	2,030	2,027	2,021	2,013	2,008	2,004	1,999	1,995	1,914

Relative risk reduction:

FF/UMEC/VI vs UMEC/VI

28%

HR 0.72
(95% CI, 0.53–0.99)

P = 0.042

FF/VI vs UMEC/VI

18%

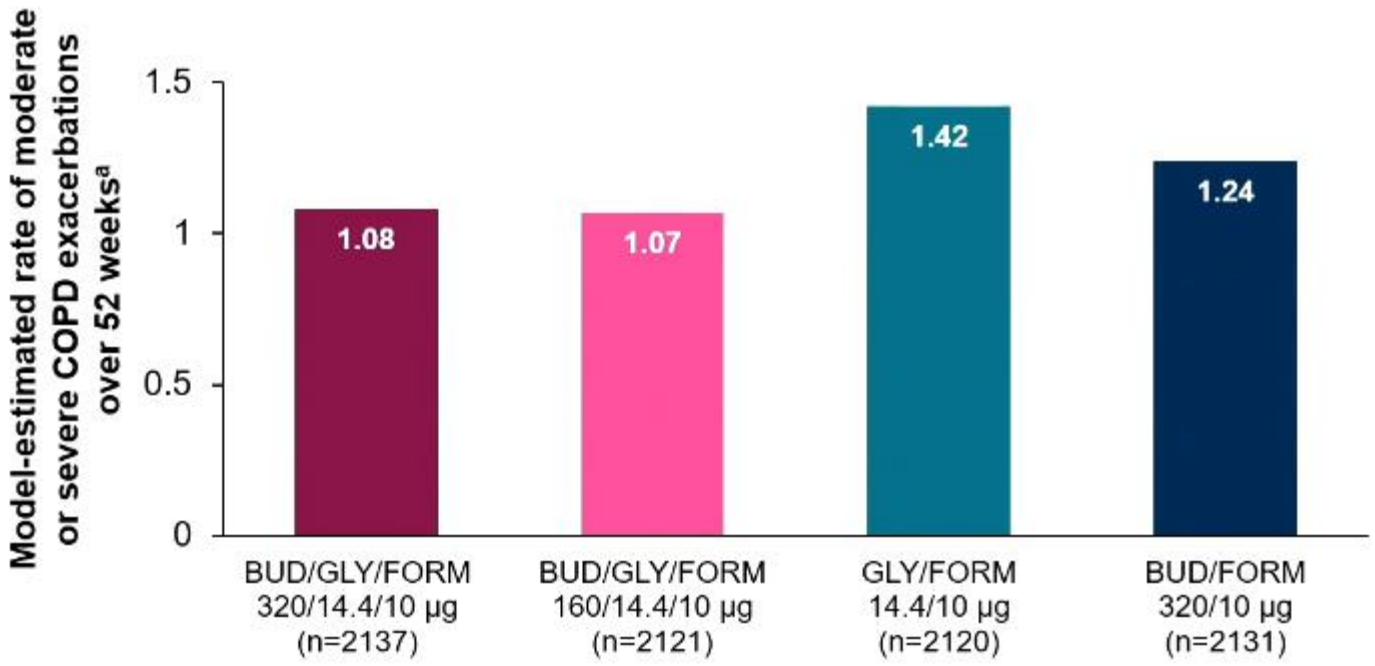
HR 0.82
(95% CI, 0.60–1.11)

P = 0.190

Am J Respir Crit Care Med Vol 201, Iss 12, pp 1508–1516, Jun 15, 2020

ETHOS BUD/GLY/FORM: the Rate of Moderate or Severe Exacerbations vs. Dual Therapies

Primary Endpoint



Over 52 weeks
BUD/GLY/FORM 320/14.4/10 µg
demonstrated a:

24% **significant reduction in exacerbation rate vs. LAMA/LABA**

13% **significant reduction in exacerbation rate vs. ICS/LABA**

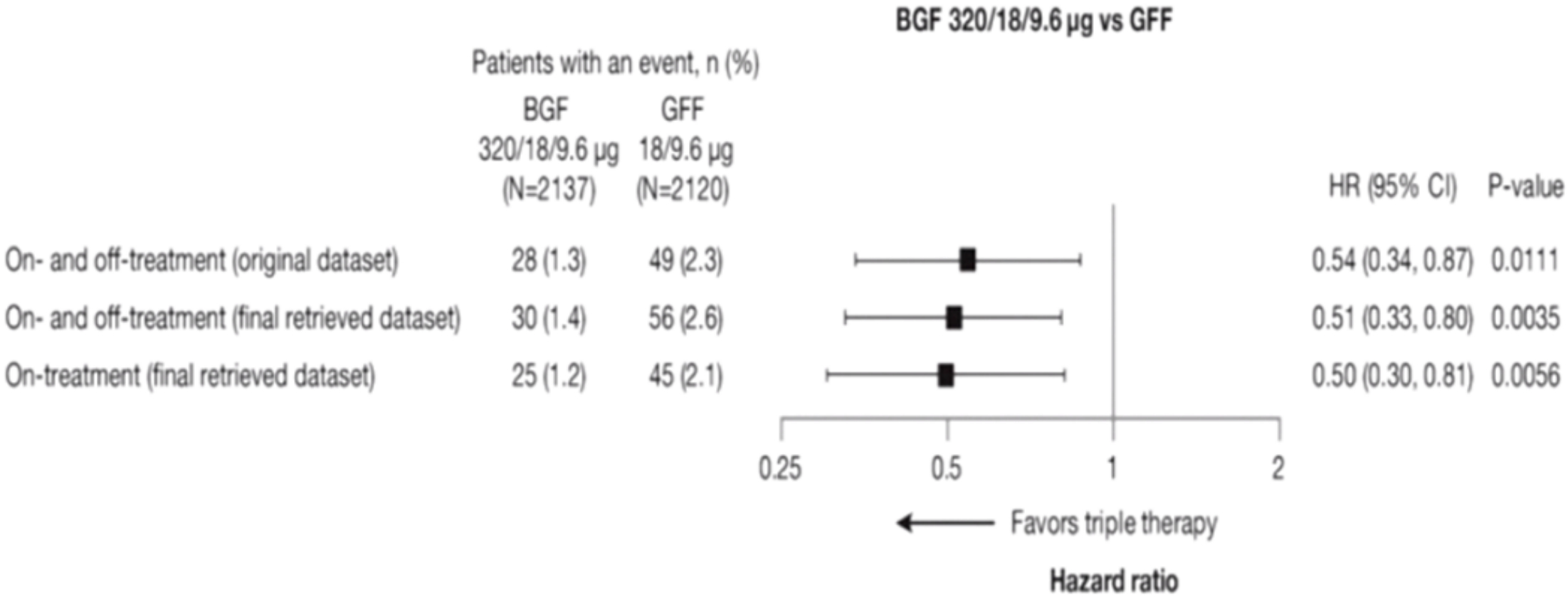
	vs. LAMA/LABA	vs. ICS/LABA
320 µg	**1.08 vs 1.42; RR: 0.76 95% CI: 0.69 to 0.83; p<0.001**	**1.08 vs 1.24; RR: 0.87 95% CI: 0.79 to 0.95; p=0.003**
160 µg	1.07 vs 1.42; RR: 0.75 95% CI: 0.69 to 0.83; p<0.001	1.07 vs 1.24; RR: 0.86 95% CI: 0.79 to 0.95; p=0.002

Notes: All treatments were administered BID. Results for moderate/severe exacerbation rate using the attributable estimand (secondary endpoint) were similar to those for the primary analysis. BUD/GLY/FORM 160/14.4/10 µg is currently not registered (off label).

[a]mITT population.

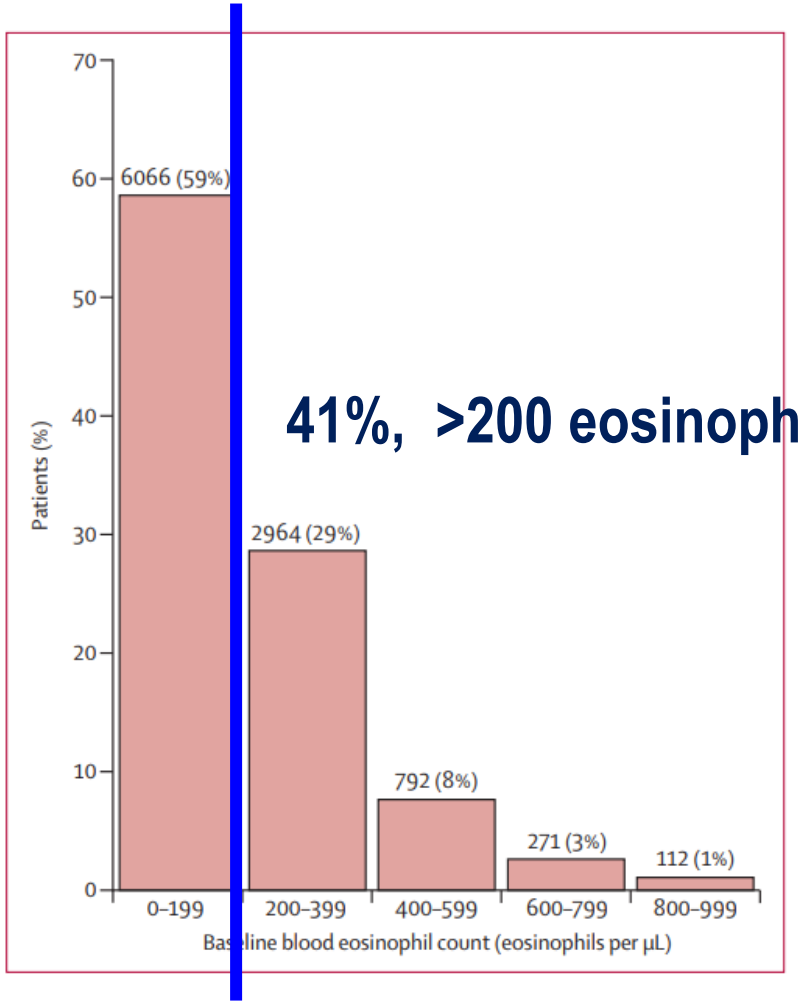
Rabe KF et al. N Engl J Med. 2020. Jul 2;383(1):35-48

All cause mortality (ACM) in the ETHOS study



Martinez FJ;American Thoracic Society;2020;1-50

Blood eosinophils and treatment response with triple and dual combination therapy in chronic obstructive pulmonary disease: analysis of the IMPACT trial

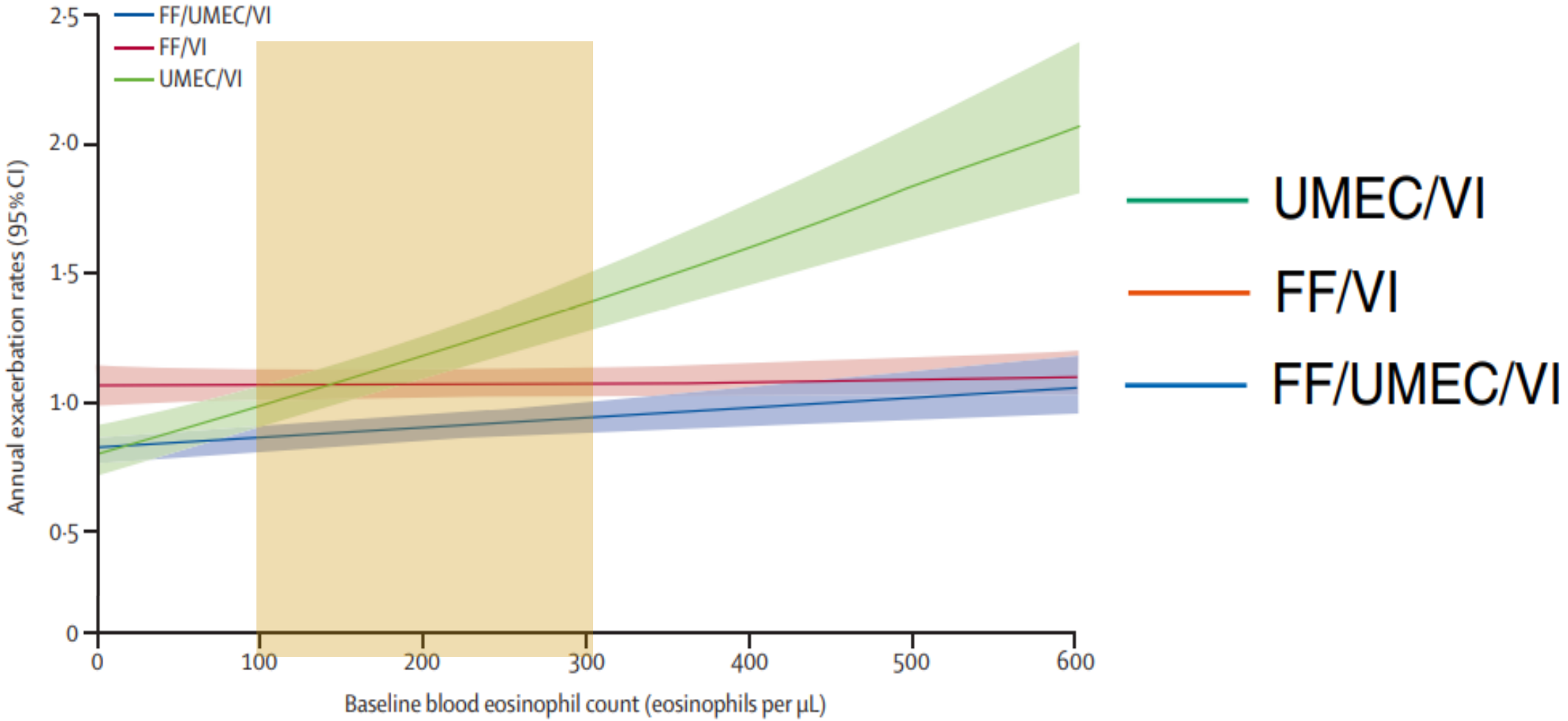


41%, >200 eosinophils/ uL

57%, >150 eosinophils/ uL

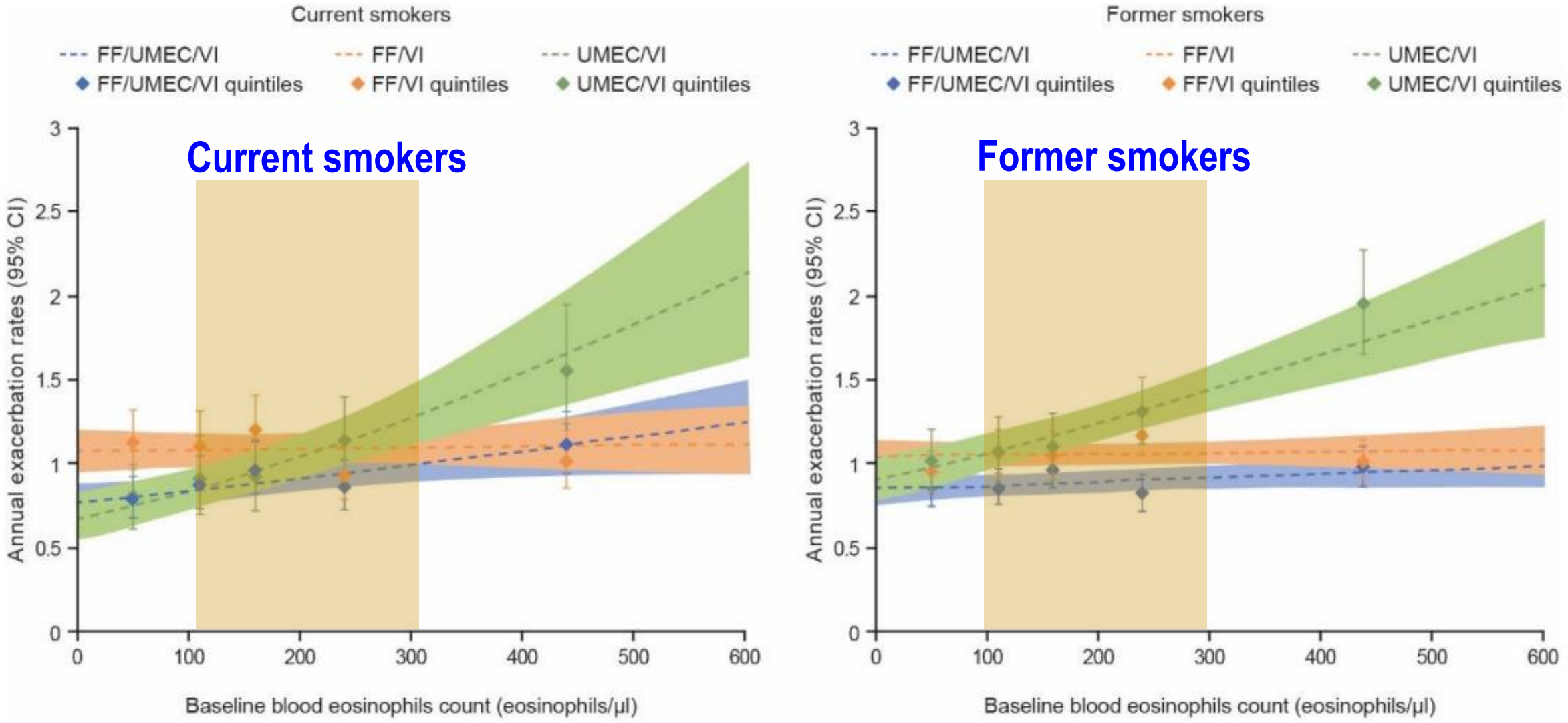
Lancet Respir Med 2019; 7: 745–56

Annual rates of moderate or severe exacerbations, by baseline blood eosinophil count



Lancet Respir Med 2019; 7: 745–56

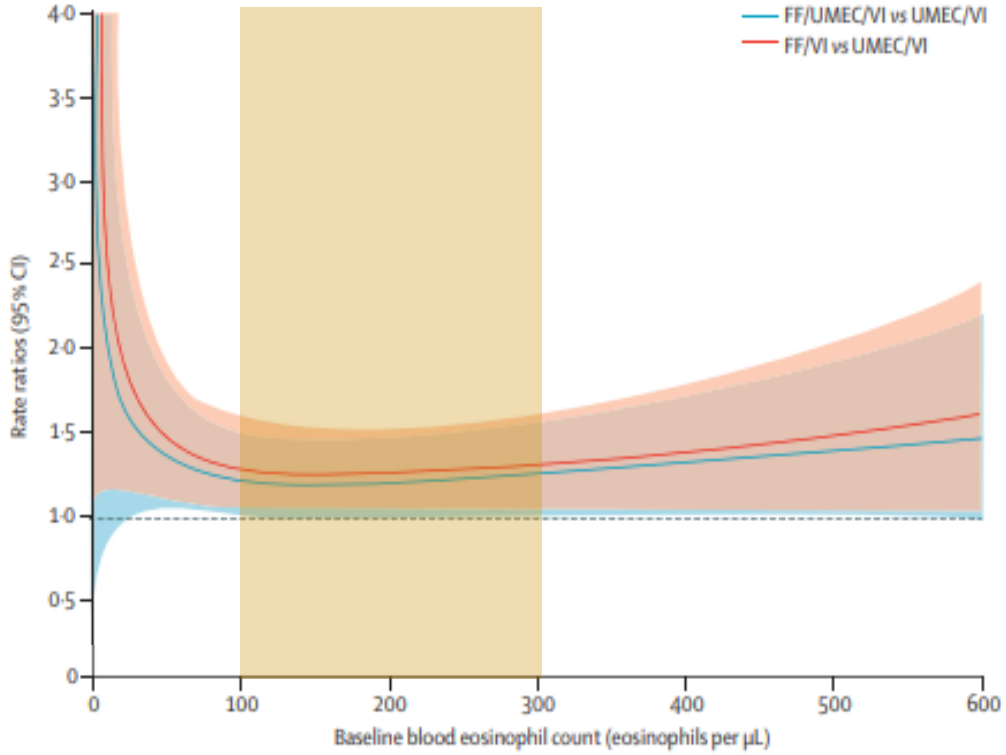
Annual rates of moderate/severe exacerbations by baseline blood eosinophil count, smoking status and individual treatment



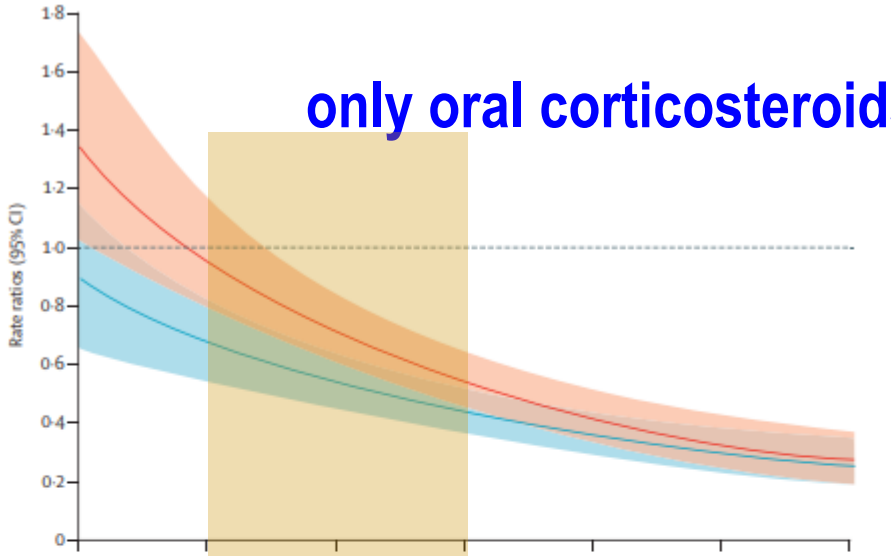
Lancet Respir Med 2019; 7: 745–56

Between-treatment differences in moderate or severe exacerbations requiring only antibiotics or oral corticosteroids, by baseline blood eosinophil count

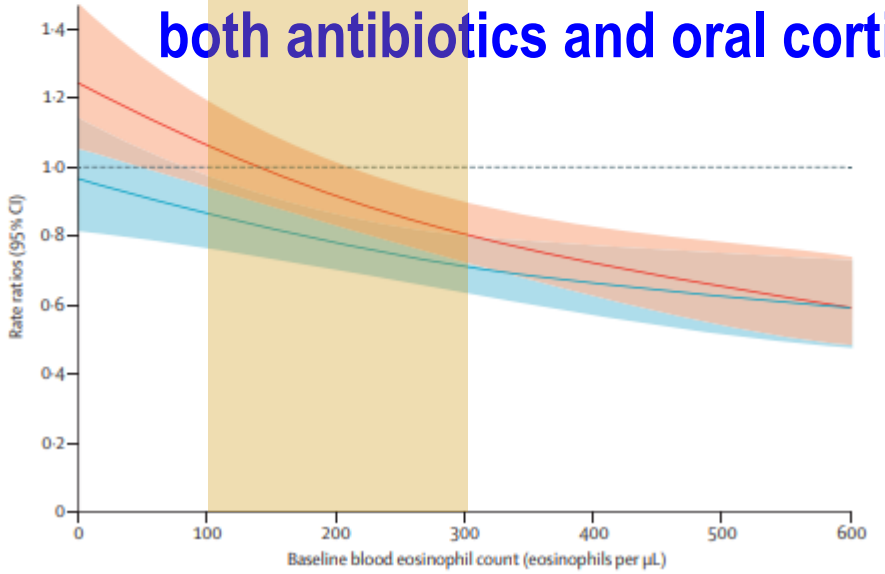
requiring only antibiotics



only oral corticosteroids



both antibiotics and oral corticosteroids



Lancet Respir Med 2019; 7: 745–56

The effect of exacerbation history on outcomes in the IMPACT trial

- **Single moderate (1 moderate/no severe; n=3056 (30%)**
- **Frequent moderate (⩾2 moderate/no severe; n=4628 (45%)**
- **Severe (⩾1 severe/any moderate; n=2671 (26%)**

Eur Respir J 2020; 55: 1901921

Between-treatment differences in rates of moderate or severe exacerbations by baseline blood eosinophil count

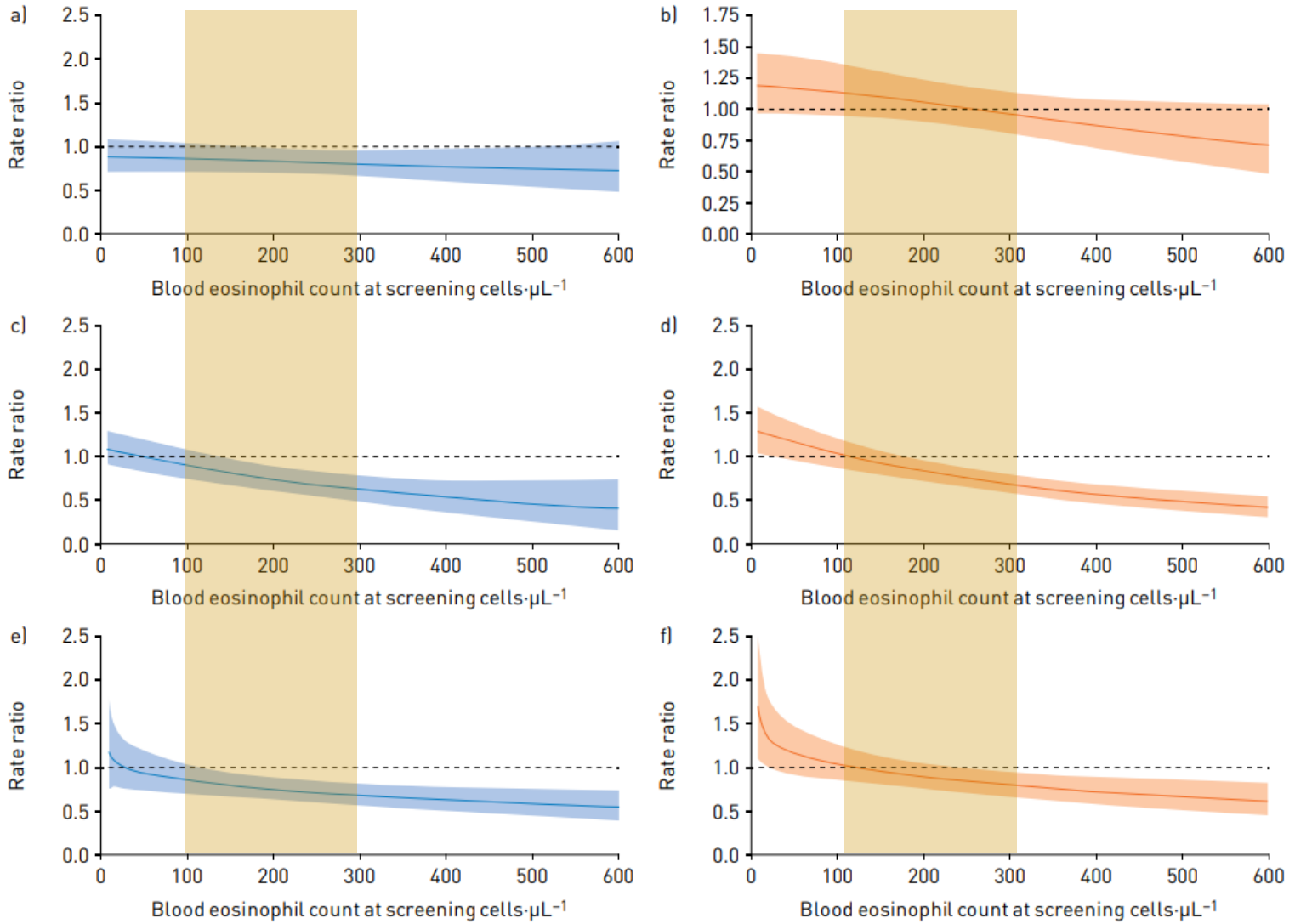
FF/UMEC/VI versus UMEC/VI

FF/VI versus UMEC/VI

single moderate

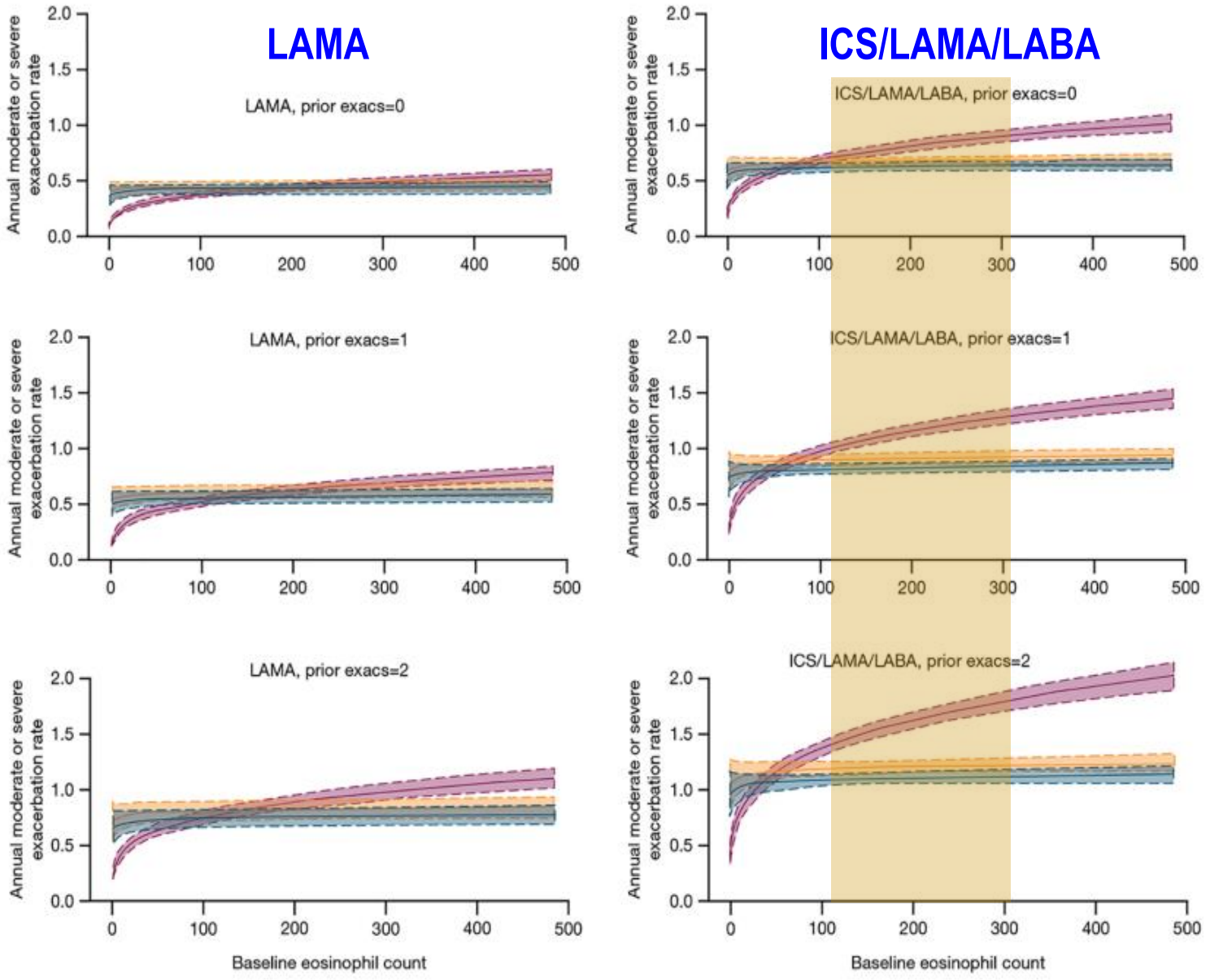
frequent moderate

severe



Predictive modeling of COPD exacerbation rates using baseline risk factors

ETHOS, KRONOS, TELOS, SOPHOS, and PINNACLE-1, PINNACLE-2, and PINNACLE-4
= 20,054 pts



Prior exacs = 0

Prior exacs = 1

Prior exacs = 2

Dave Singh et al Ther Adv Respir Dis 2022, Vol. 16: 1–15

The right treatment for the right patient with COPD: lessons from the IMPACT trial

Daiana Stolz[1] and Marc Miravitlles

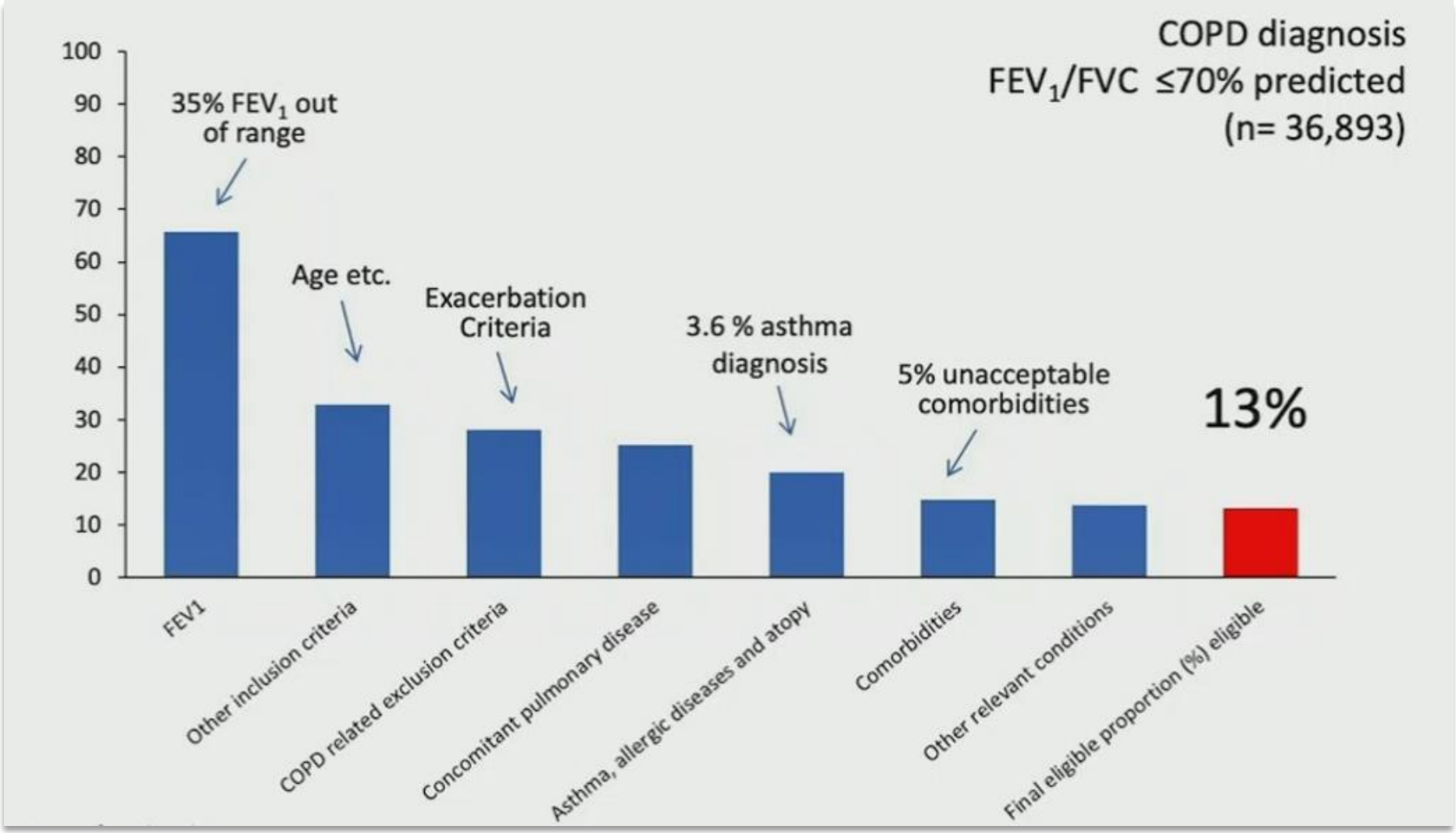
- **BEC**, **smoking status**, **previous history of exacerbations** and **type of exacerbations** modulate the response to ICS in COPD
- **Not much room for LABA/ICS** in the treatment of COPD
- No sense to add an ICS to dual bronchodilation in patients with a **BEC <100 cells/uL**
- All patients with **frequent or severe exacerbations** and a **BEC >300 cells per µL** should receive triple therapy

Eur Respir J 2020; 55: 2000881

Contents

- The evidence of single inhaler triple therapy in RCT study
- Real world evidence of single inhaler triple therapy
- The issue of Device

Patients in UK Primary Care of Dual Bronchodilator RCT Inclusion and Exclusion Criteria



Halpin DMG;Respiratory Research;2016;17;1-13

Relationships among the explanatory clinical trials, observational study, and pragmatic clinical trials

Randomization
Comparability between patient groups

Continuum

Real-world evidence
Relative **effectiveness** of treatment in the real world

Prospective, blinded explanatory clinical trial

Pragmatic randomized clinical trial

Retrospective observational study

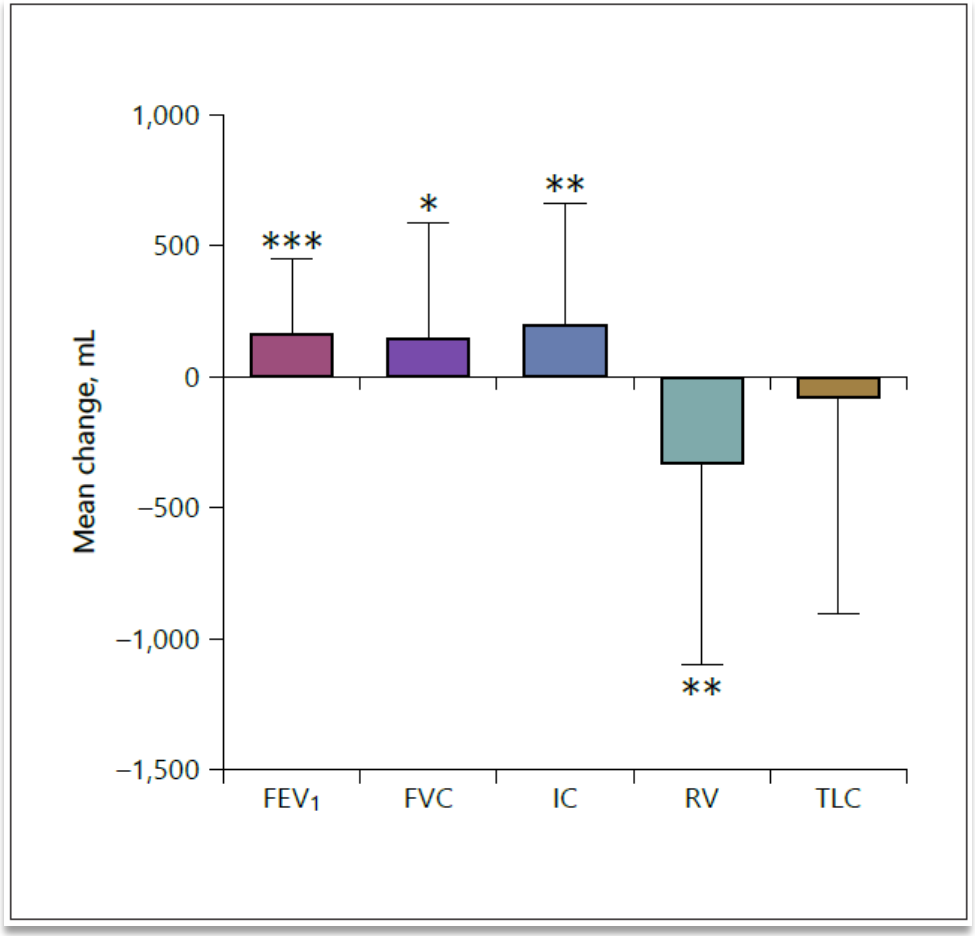
NY Jeong et, al. Cardiovasc Prev Pharmacother. 2020 Jul;2(3):85-98

Real-Life Clinical and Functional Effects of Fluticasone Furoate/Umeclidinium/Vilanterol-Combined Triple Therapy in Patients with Chronic Obstructive Pulmonary Disease

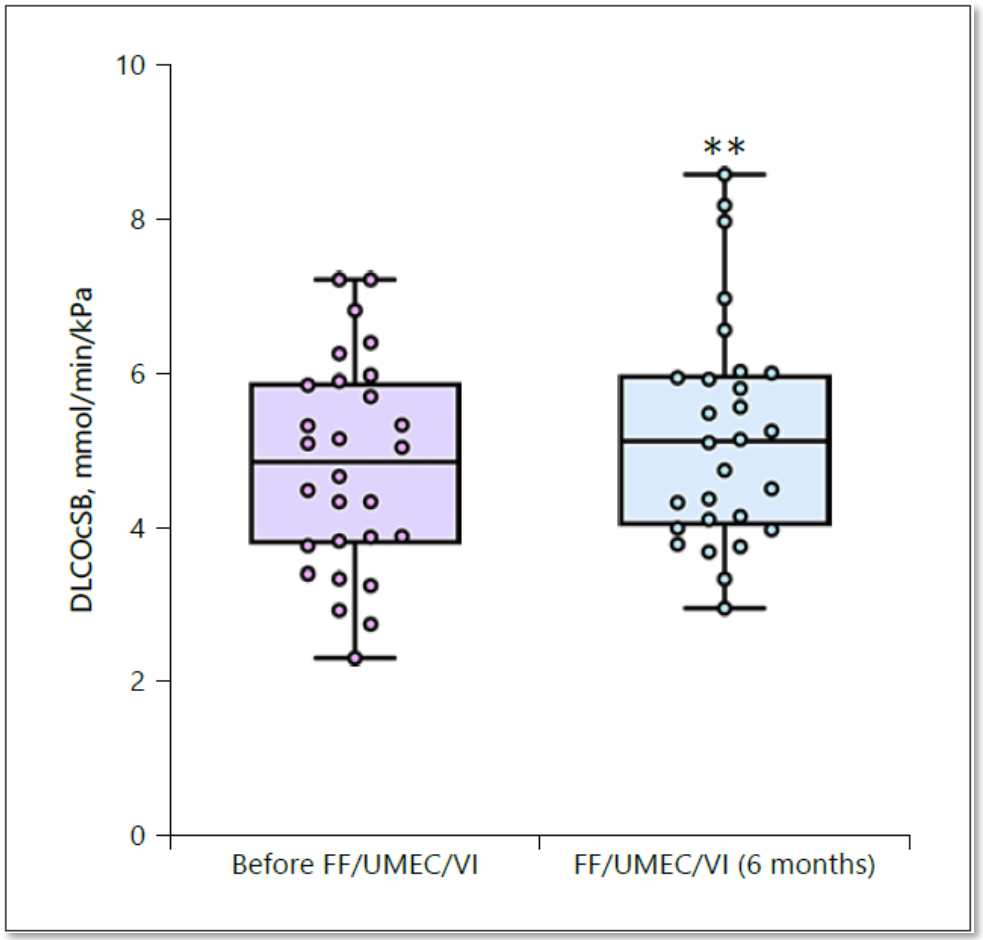
- 44 COPD patients with recurrent exacerbations
- single center, observational study

Pelaia C. Respiration 2021; 100: 127-134.

Mean change of FEV1, FVC, IC, RV, and TLC after 24 weeks of combined triple therapy



Effect of FF/UME/VI on DLCO



Pelaia C. Respiration 2021; 100: 127-134.

Summary of effectiveness outcomes

	Before FF/UMEC/VI	FF/UMEC/VI (6 months)	*p* value
mMRC dyspnea scale, median (IQR)	3 (3–4)	2 (1–3)	**<0.0001**
CAT score, mean (±SD)	23.30 (±9.289)	14.15 (±9.578)	**<0.0001**
FEV_1, mean (±SD), L	1.369 (±0.4543)	1.540 (±0.4924)	**<0.001**
RV, median (IQR), L	3.245 (2.658–4.138)	3.175 (2.470–3.873)	**<0.01**
FEF_{25-75}, median (IQR), L/s	0.6450 (0.3775–1.005)	0.7750 (0.5250–1.070)	**<0.0001**
TLC, mean (±SD), L	6.289 (±1.557)	6.203 (±1.511)	0.4932
IC, mean (±SD), L	1.907 (±0.6841)	2.114 (±0.6427)	**<0.01**
FVC, mean (±SD), L	2.323 (±0.6552)	2.475 (±0.6580)	**<0.05**
PEF, mean (±SD), L/s	4.125 (±1.346)	4.823 (±1.639)	**<0.0001**
DLCOcSB, mean (±SD), mmol/min/kPa	4.808 (±1.365)	5.224 (±1.466)	**<0.01**
COPD exacerbations, mean (±SD), *N*	4.815 (±2.185)	2.344 (±2.252)	**<0.001**

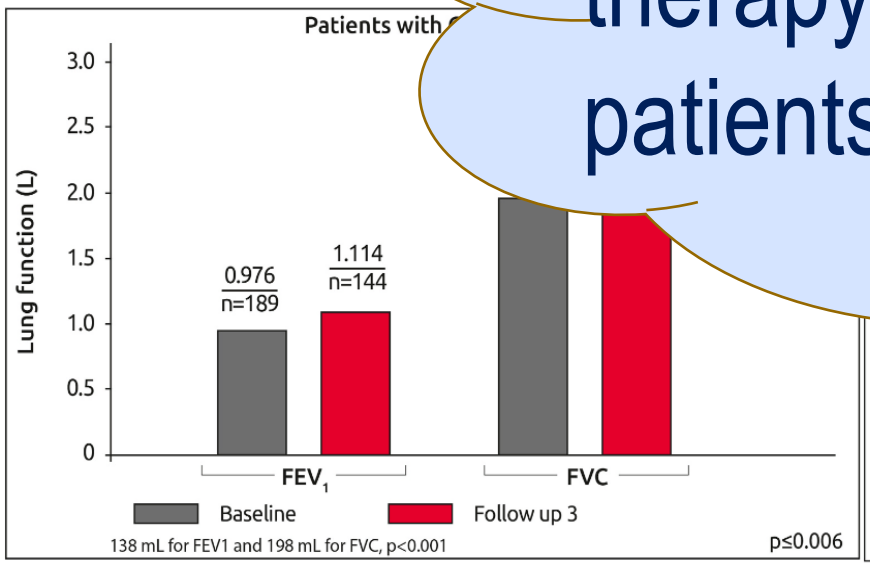
Pelaia C. Respiration 2021; 100: 127-134.

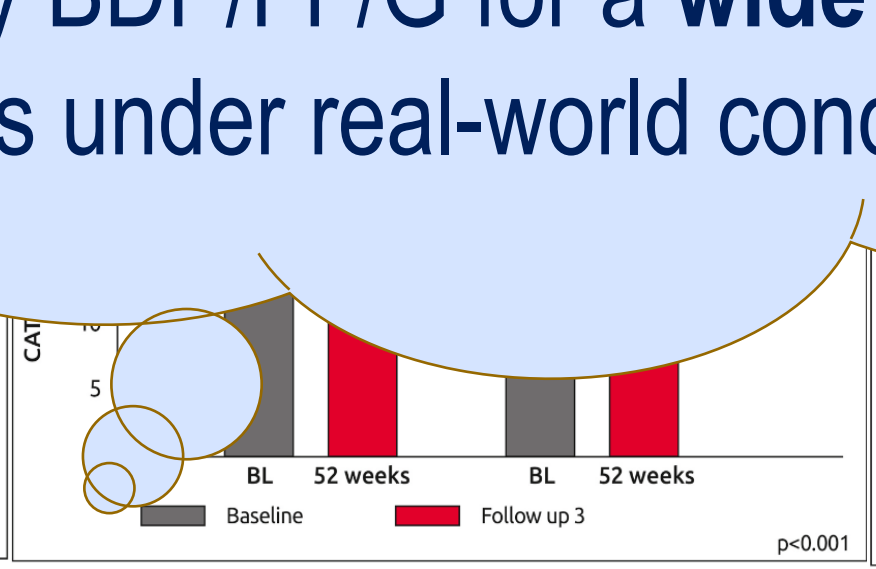
TRICOP – A Real-world effectiveness study with a single-inhaler extrafine triple therapy over 52 weeks in Austrian patients with COPD

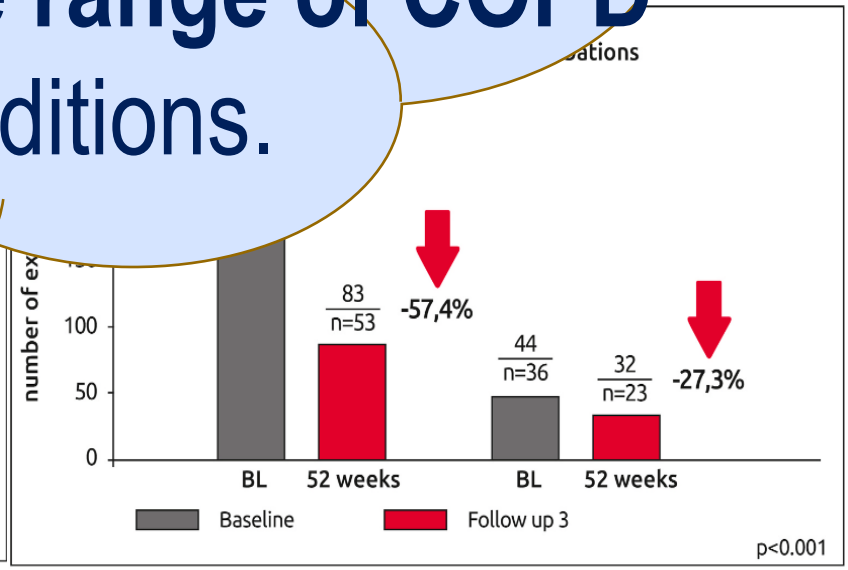
- **non-interventional study**
- **265 patients with mod**
  and persister

46.8

These results provide evidence of effectiveness of the extrafine fixed-dose triple therapy BDP/FF/G for a **wide range of COPD** patients under real-world conditions.







Respiratory Medicine 182 (2021) 106398

INTREPID: single- *versus* multiple-inhaler triple therapy for COPD in usual clinical practice

David M.G. Halpin[1], Sally Worsley[2], Afisi S. Ismaila[3,4], Kai-Michael Beeh[5], Dawn Midwinter[6], Janwillem W.H. Kocks[7,8,9], Elaine Irving[2], Jose M. Marin [iD][10,11], Neil Martin[12,13], Maggie Tabberer[14], Neil G. Snowise[12,15] and Chris Compton[16]

- **FF/UMEC/VI Ellipta (N=1545)**
- **Non-Ellipta MITT (N=1547)**

Halpin DMG; ERJ Open Research;2021;1-46

The Clinical Effectiveness of Fluticasone Furoate/Umeclidinium Bromide/Vilanterol in a **Single** Inhaler (ELLIPTA)* when Compared with Non-ELLIPTA **Multiple** Inhaler Triple Therapies (MITT) in COPD Patients Within a Usual Care Setting

INTREPID

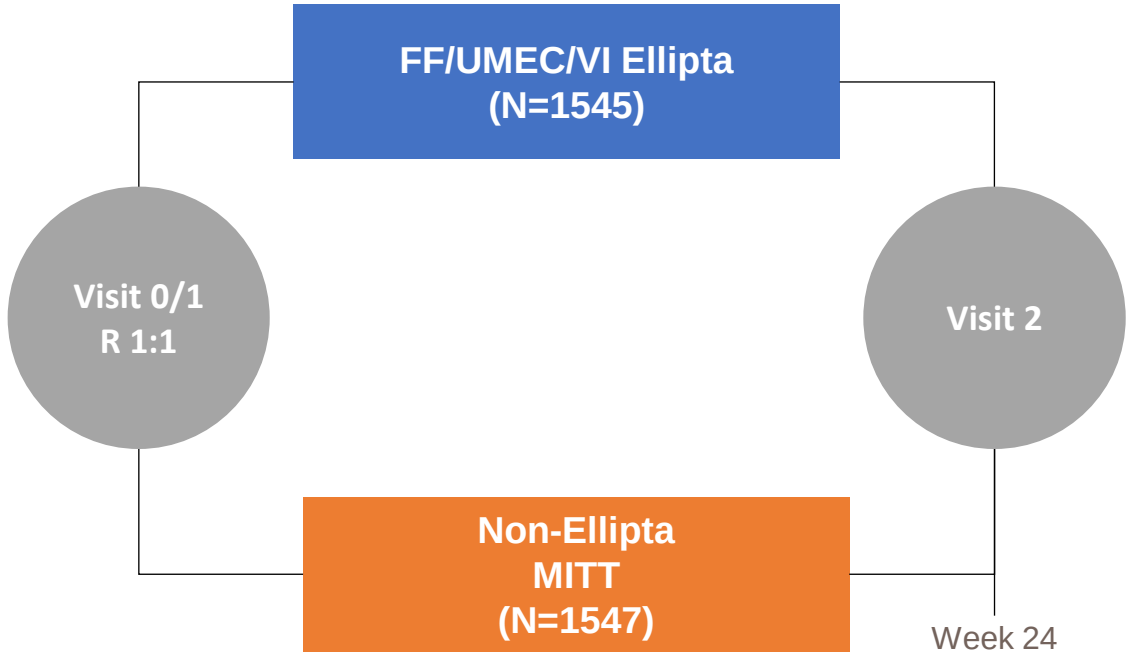
INVESTIGATION OF
TRELEGY
EFFECTIVENESS USUAL
PRACT**I**CE
DESIGN

- Sweden
- United Kingdom
- Netherlands
- Germany
- Spain

Reference: Halpin DMG;ERJ Open Research;2021;1-46

Study design

Randomised, **open-label, parallel-group, multicentre, effectiveness Phase IV study** of **24-weeks** duration stratified by prior medication group



Patient population

- ≥40 years of age and documented physician diagnosis of COPD
- **At least one moderate/severe COPD exacerbation in the 3 years** prior to randomisation
- Patients receiving at least 16 weeks prior to randomisation non-Ellipta MITT or LAMA+LABA or ICS+LABA
- CAT ≥10

Limited exclusion criteria

- Recent history of life-threatening conditions
- Patients with resolution of an exacerbation <2 weeks prior to first visit
- Long-term use of oral corticosteroids

EU Effectiveness Study

Halpin DMG;ERJ Open Research;2021;1-46

Study design: Endpoints

Primary endpoint

Proportion of **responders based on the CAT** at Week 24. Response defined as reduction from baseline of **≥2** points in CAT score at 24 weeks

Secondary endpoints

- **Change from baseline in FEV_1** at 24 weeks (in a subset of participants)
- Percentage of participants making at least **1 critical error** in inhalation technique at 24 weeks (in a subset of participants)

Safety

Examination of all SAEs, treatment-related AEs and AEs that lead to withdrawal from study or study treatment

- Other non-SAEs were not collected

Other endpoints

- Proportion of responders who experience a CID
- Annualised rate of moderate/severe exacerbations
- Time to first moderate/severe exacerbation

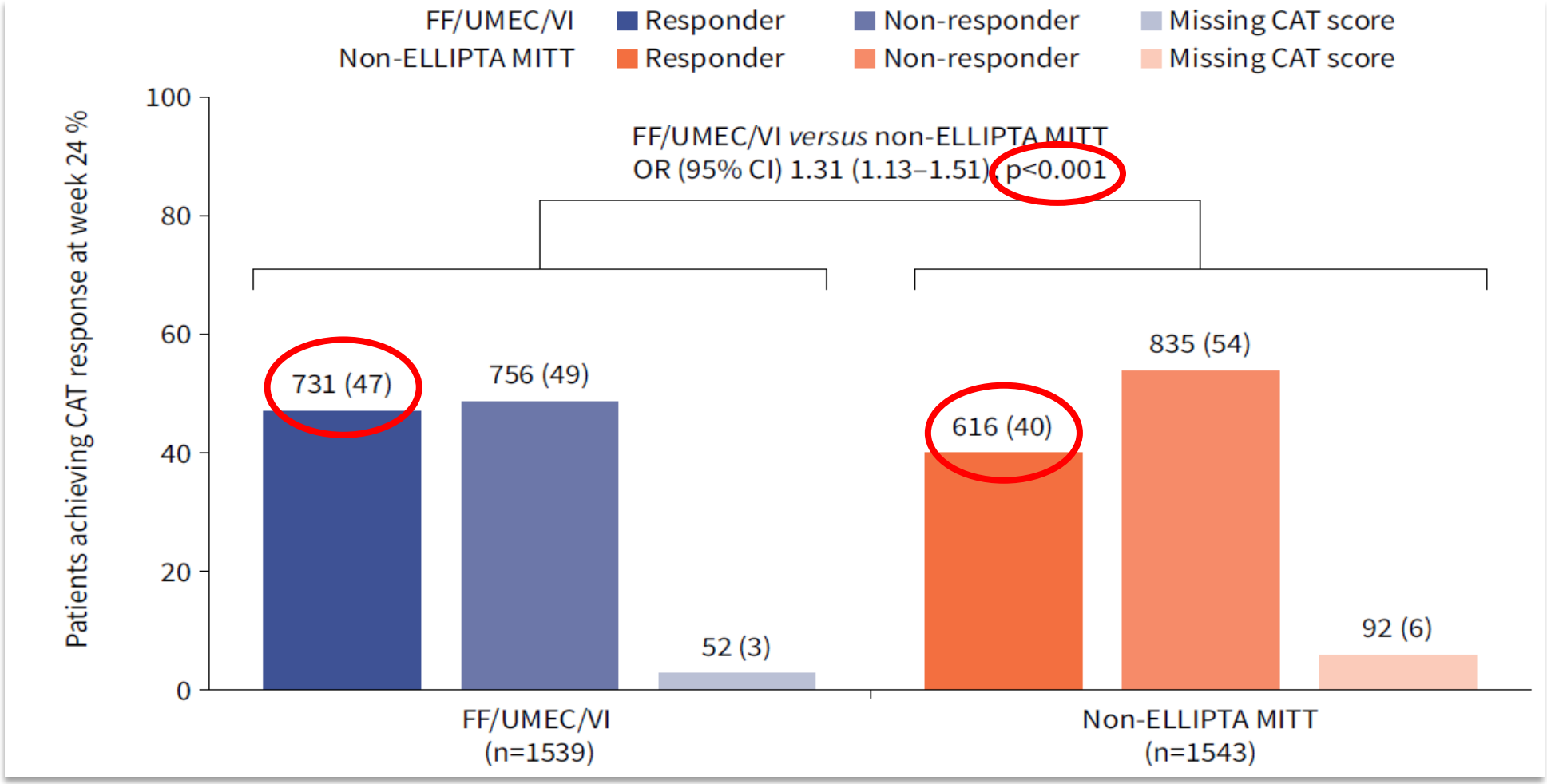
1. Halpin DMG;ERJ Open Research;2021;1-46
2. Worsley S;ERJ Open Research;2019;5;1-9

Summary of baseline demographics and disease characteristics

ITT population	FF/UMEC/VI (N=1545)	Non-Ellipta MITT (N=1547)	Total (N=3092)
Age (years), mean (SD)	67.8 (8.78)	67.8 (8.59)	67.8 (8.68)
Sex (% male)	837 (54%)	818 (53%)	1655 (54%)
Post-bronchodilator FEV_1 (L) (FEV_1 population)			
n	825	827	1652
Mean (SD)	1.474 (0.5653)	1.462 (0.5840)	1.468 (0.5746)
Post-bronchodilator percent predicted FEV_1, mean (SD) %	54.1 (18.49)	54.1 (18.58)	54.1 (18.53)
Reversibility to salbutamol, n (%)	174 (22)	186 (24)	360 (23)
Patients with moderate/severe COPD exacerbations			
0	**363 (23%)**	**361 (23%)**	**724 (23%)**
1	**615 (40%)**	**610 (39%)**	**1225 (40%)**
≥2	567 (37%)	576 (37%)	1143 (37%)
CAT score at screening			
n, mean (SD)	1543, 20.8 (6.76)	1547, 20.5 (6.62)	3090, 20.7 (6.69)
Prior medication use (Actual strata)			
ICS+LAMA+LABA	1226 (79%)	1235 (80%)	2461 (80%)
ICS+LABA	126 (8%)	126 (8%)	252 (8%)
LABA+LAMA	192 (12%)	183 (12%)	375 (12%)
Missing	1 (<1%)	3 (<1%)	4 (<1%)

Halpin DMG;ERJ Open Research;2021;1-46

Primary effectiveness endpoint % CAT responders at week 24: Primary endpoint (ITT population)



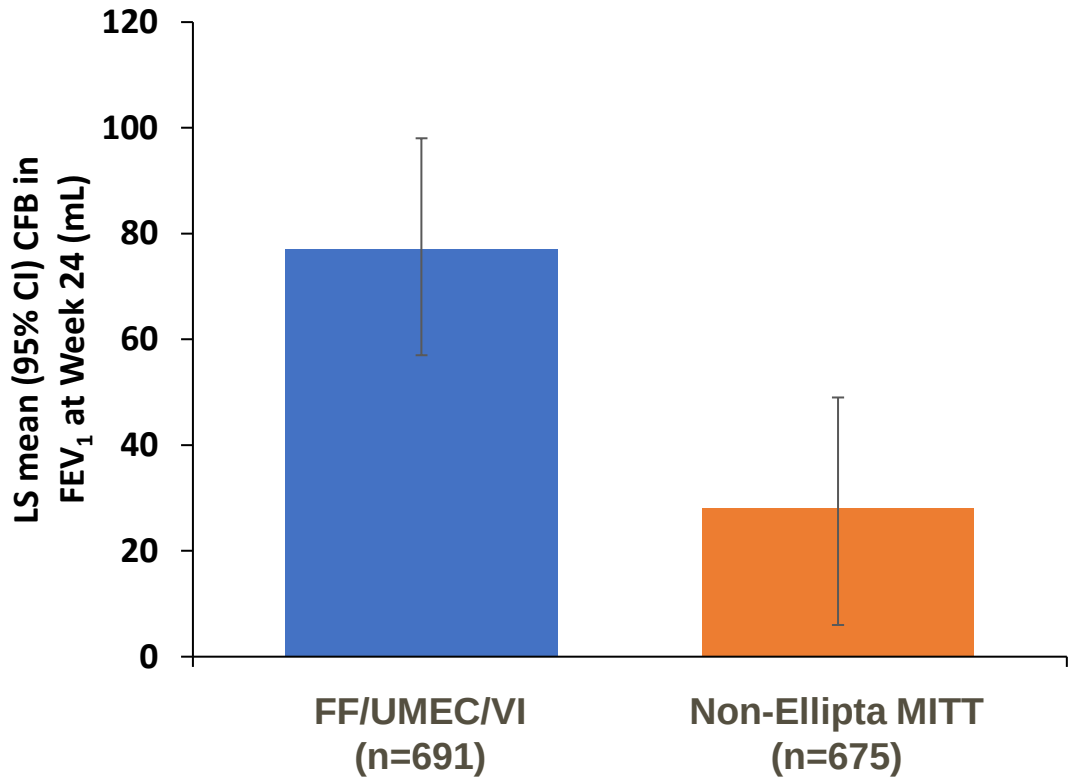
*Response defined as a CAT score of 2 units below baseline or lower.

Reference: Halpin DMG;ERJ Open Research;2021;1-46

FF/UMEC/VI significantly improved lung function versus non-ELLIPTA MITT at Week 24

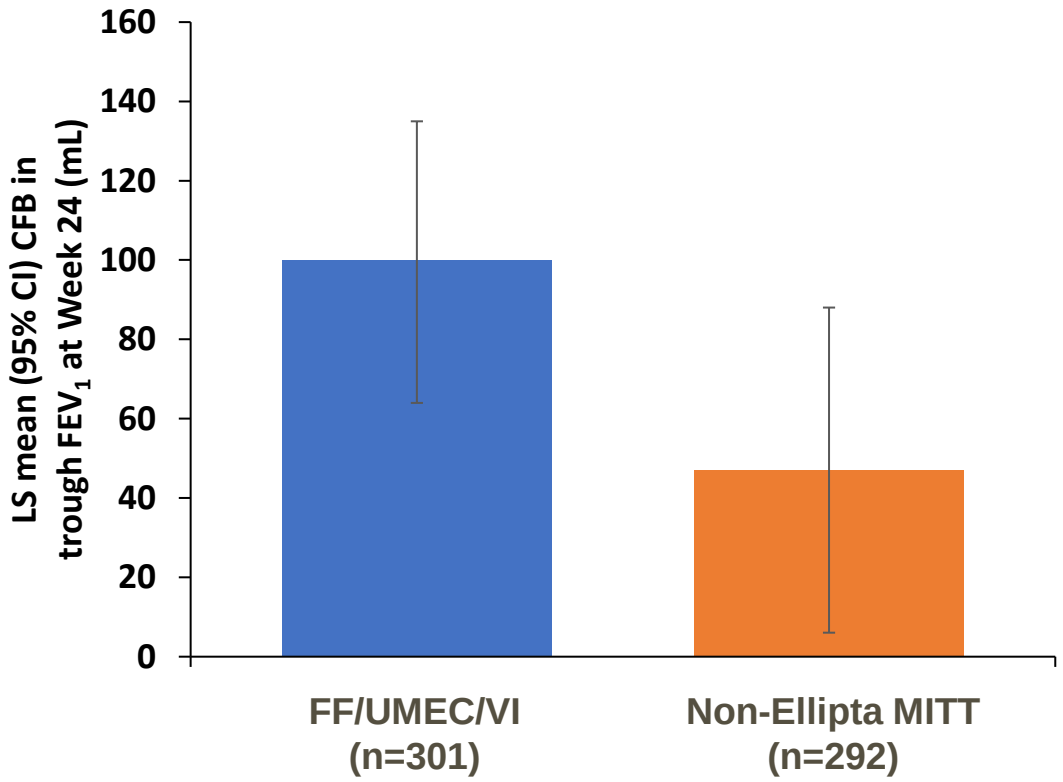
FEV_1

Difference (95% CI): 50 mL (26, 73); **P<0.001**



Trough FEV_1

Difference (95% CI): 53 mL (9, 96); **P=0.017**

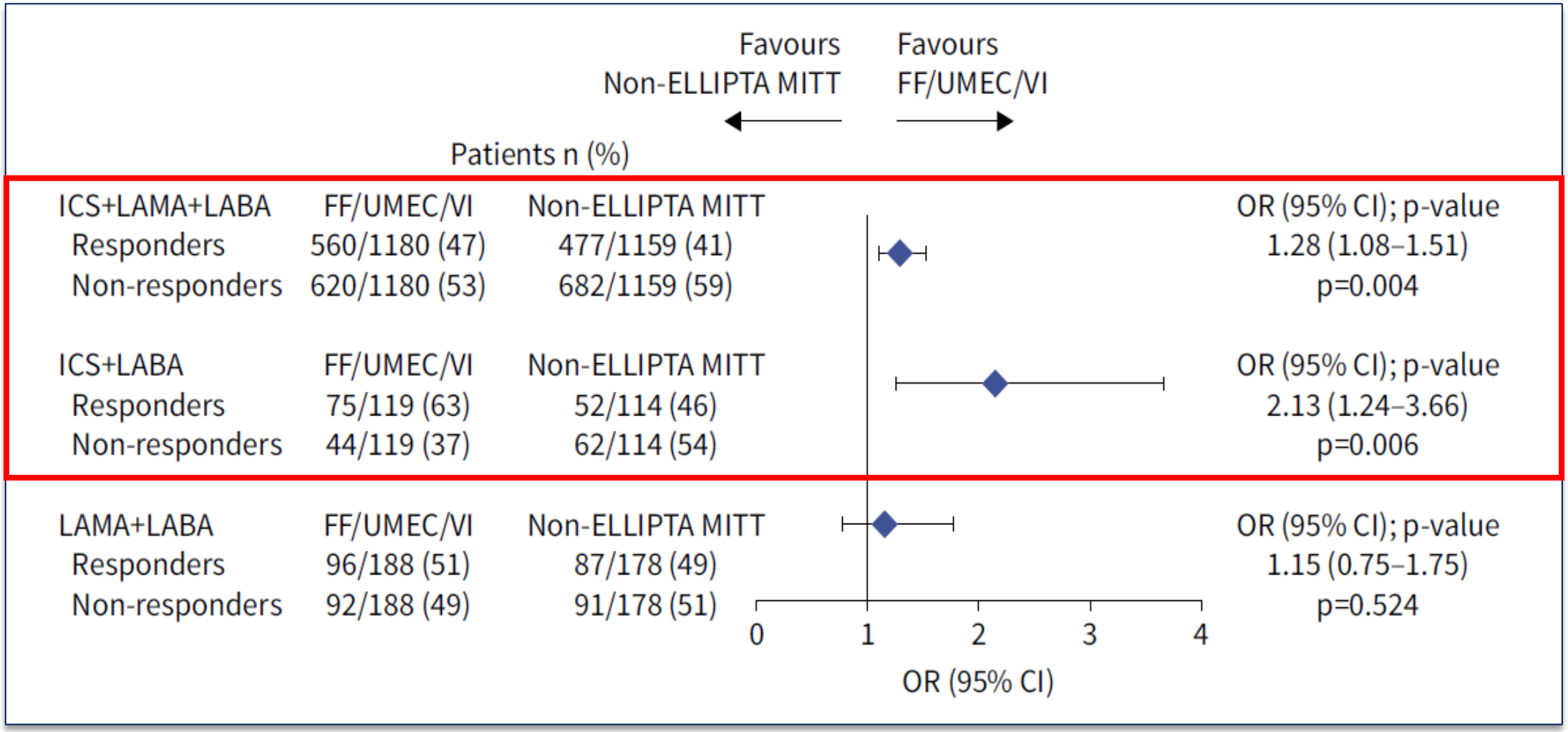


Halpin DMG;ERJ Open Research;2021;1-46

CFB, change from baseline; CI, confidence interval; FEV1, forced expiratory volume in 1 second; FF, fluticasone furoate; LS, least square; MITT, multiple-inhaler triple therapy; UMEC, umeclidinium; VI, vilanterol.

Consistent treatment effect across prior medication strata

CAT responders at Week 24 by actual prior medication strata



Halpin DMG;ERJ Open Research;2021;1-46

INTREPID : Conclusions

Single-inhaler FF/UMEC/VI resulted in significantly more patients achieving **health status improvement** and **greater lung function** benefit versus **non-ELLIPTA MITT**

This pragmatic study broadens the understanding of the **effectiveness of FF/UMEC/VI beyond the traditional RCT** setting, into real-world clinical practice

Halpin DMG;ERJ Open Research;2021;1-46

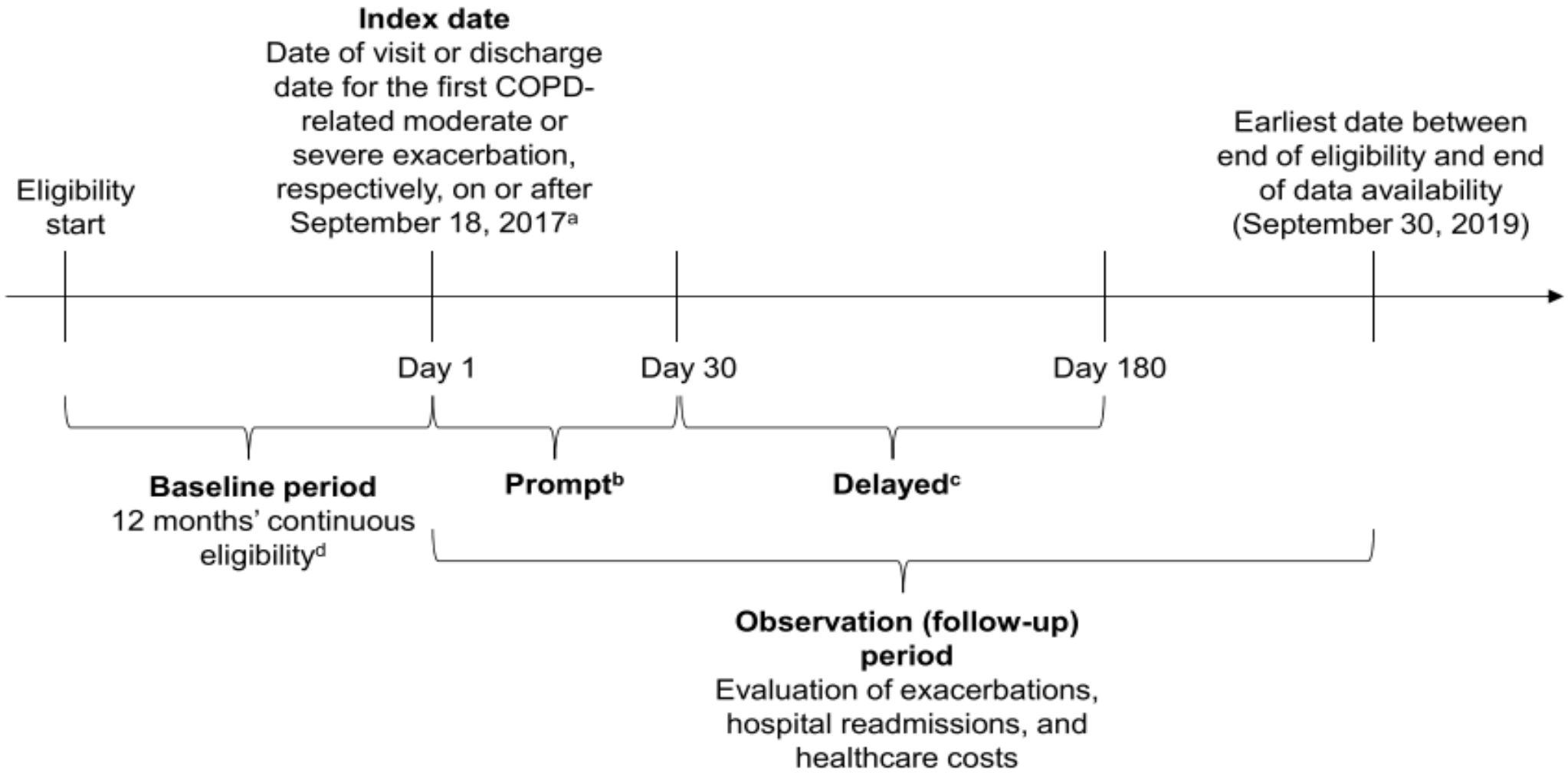
Benefit of Prompt versus Delayed Use of Single-Inhaler Fluticasone Furoate/Umeclidinium/ Vilanterol (FF/UMEC/VI) Following a COPD Exacerbation

David Mannino[1], Michael Bogart[2], Guillaume Germain[3], Shirley P Huang[2], Afisi S Ismaila[4,5], François Laliberté[3], Young Jung[3], Sean D MacKnight[3], Marjorie A Stiegler[6,7], Mei Sheng Duh[8]

Patients and Methods: This retrospective cohort study used data from the IQVIA PharMetrics® Plus database. Patients initiating FF/UMEC/VI following a COPD exacerbation between September 18, 2017 and September 30, 2019 (exacerbation = index date) were categorized as prompt (within 30 days of index) or delayed (31–180 days after index) FF/UMEC/VI initiators. Patients were aged ≥40

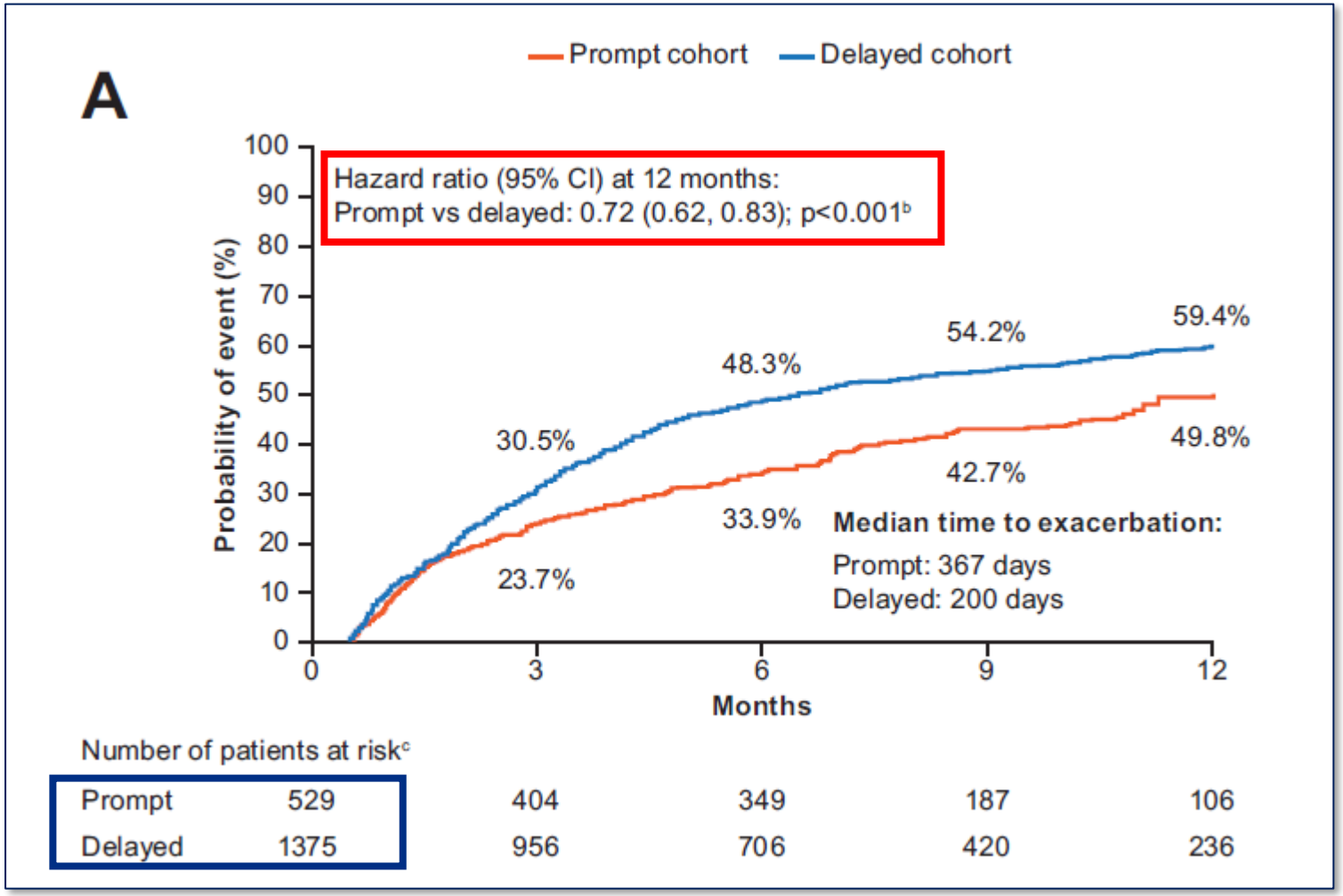
healthcare claims database across all 50 states in the US, **N=870,384**

International Journal of Chronic Obstructive Pulmonary Disease 2022:17 491–504



International Journal of Chronic Obstructive Pulmonary Disease 2022:17 491–504

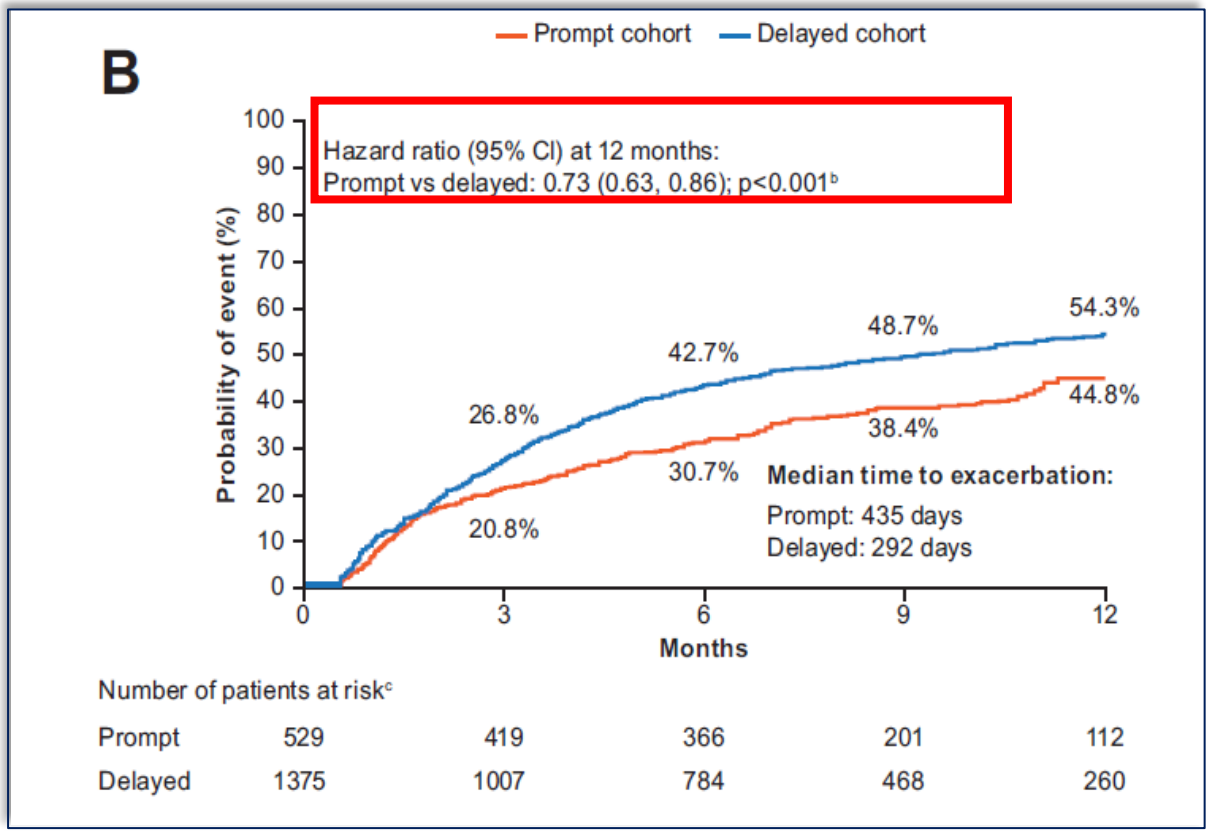
Time to first COPD exacerbation (Overall)



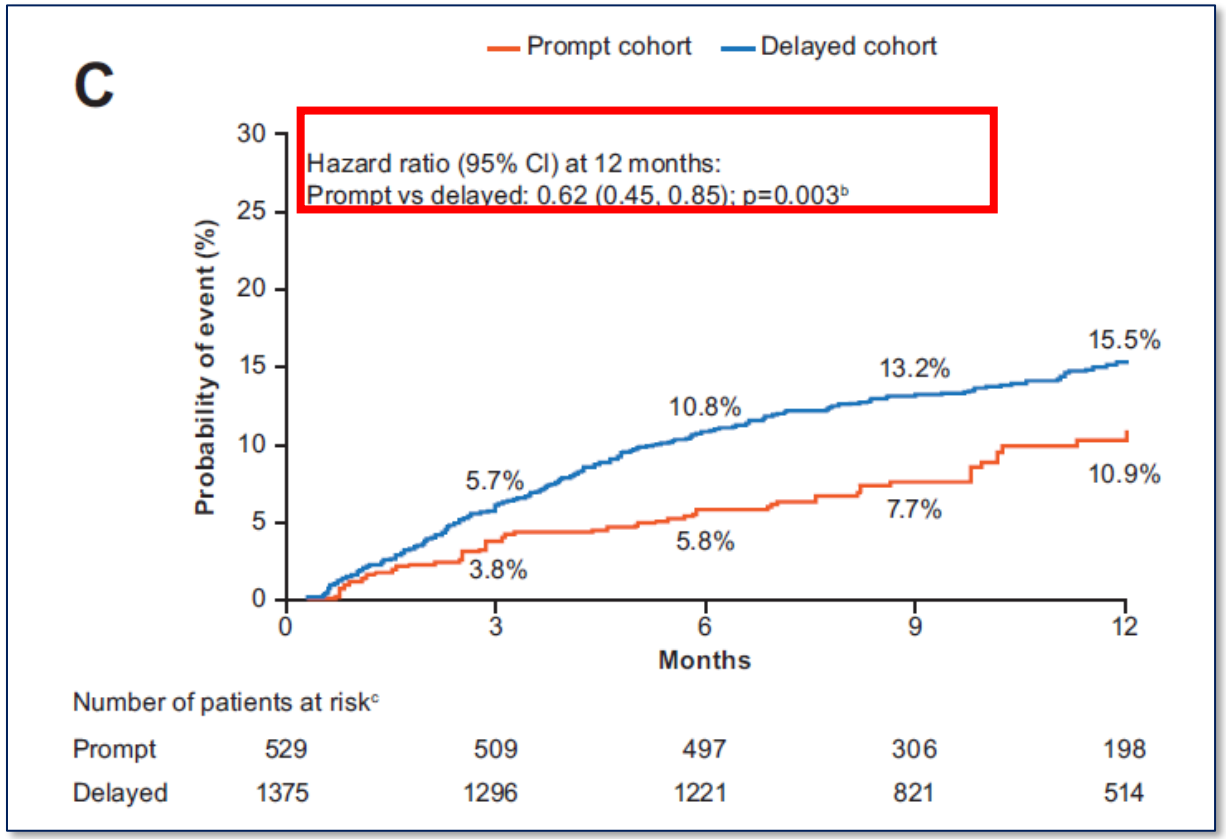
International Journal of Chronic Obstructive Pulmonary Disease 2022:17 491–504

Time to first COPD exacerbation

moderate



severe exacerbation

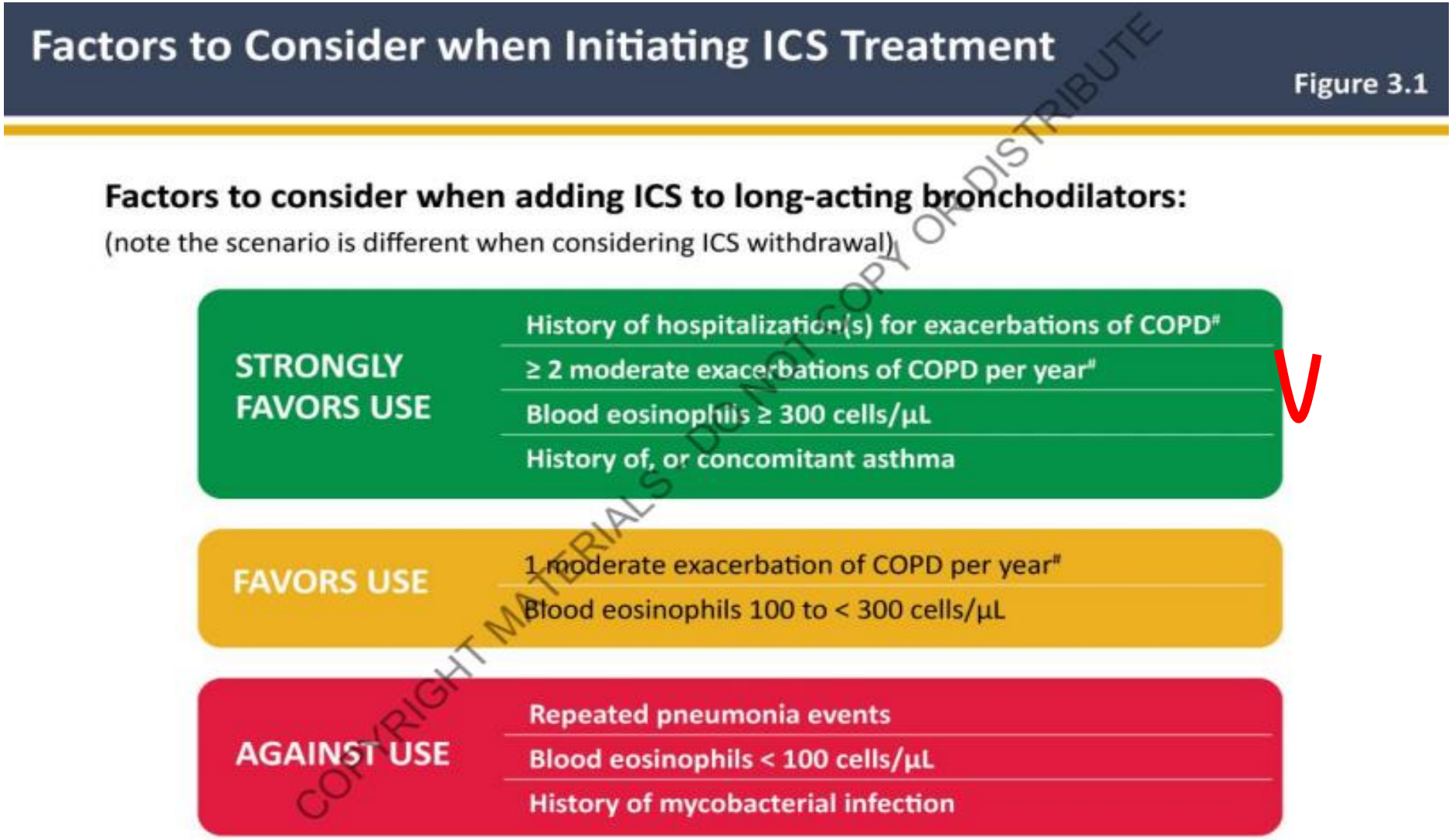


International Journal of Chronic Obstructive Pulmonary Disease 2022:17 491–504

ICS-containing therapy in COPD

LABA/LAMA *vs* LABA/LAMA/ICS

GOLD 2023 recommendations



Factors to Consider when Initiating ICS Treatment

Figure 3.1

Factors to consider when adding ICS to long-acting bronchodilators:

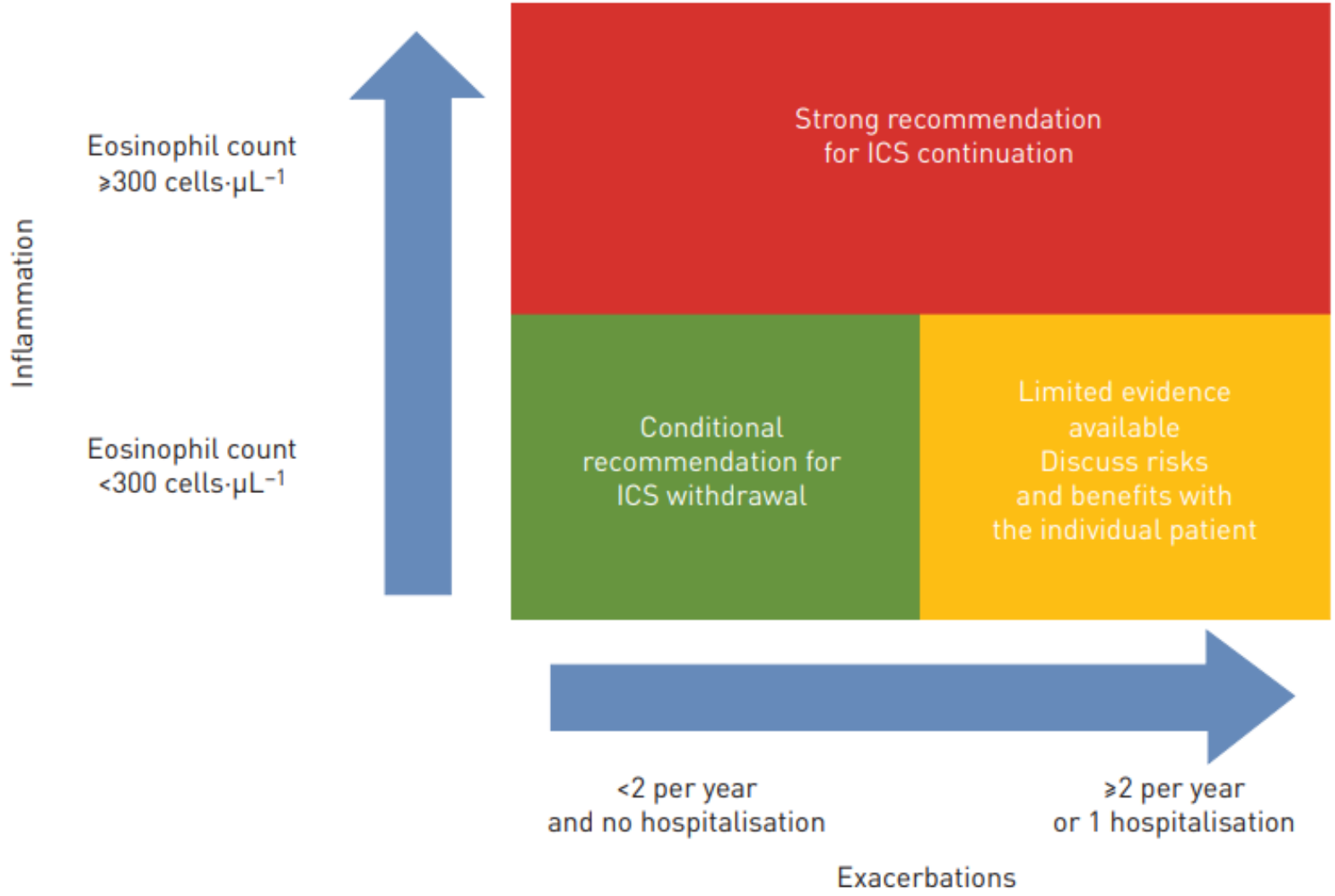
(note the scenario is different when considering ICS withdrawal)

STRONGLY FAVORS USE	History of hospitalization(s) for exacerbations of COPD[#]
	≥ 2 moderate exacerbations of COPD per year[#]
	Blood eosinophils ≥ 300 cells/µL
	History of, or concomitant asthma
FAVORS USE	1 moderate exacerbation of COPD per year[#]
	Blood eosinophils 100 to < 300 cells/µL
AGAINST USE	Repeated pneumonia events
	Blood eosinophils < 100 cells/µL
	History of mycobacterial infection

[#]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.

Adapted from & reproduced with permission of the © ERS 2019: *European Respiratory Journal 52 (6) 1801219; DOI: 10.1183/13993003.01219-2018 Published 13 December 2018*

European Respiratory Society 2020 guideline: Recommendations for withdrawal of ICS

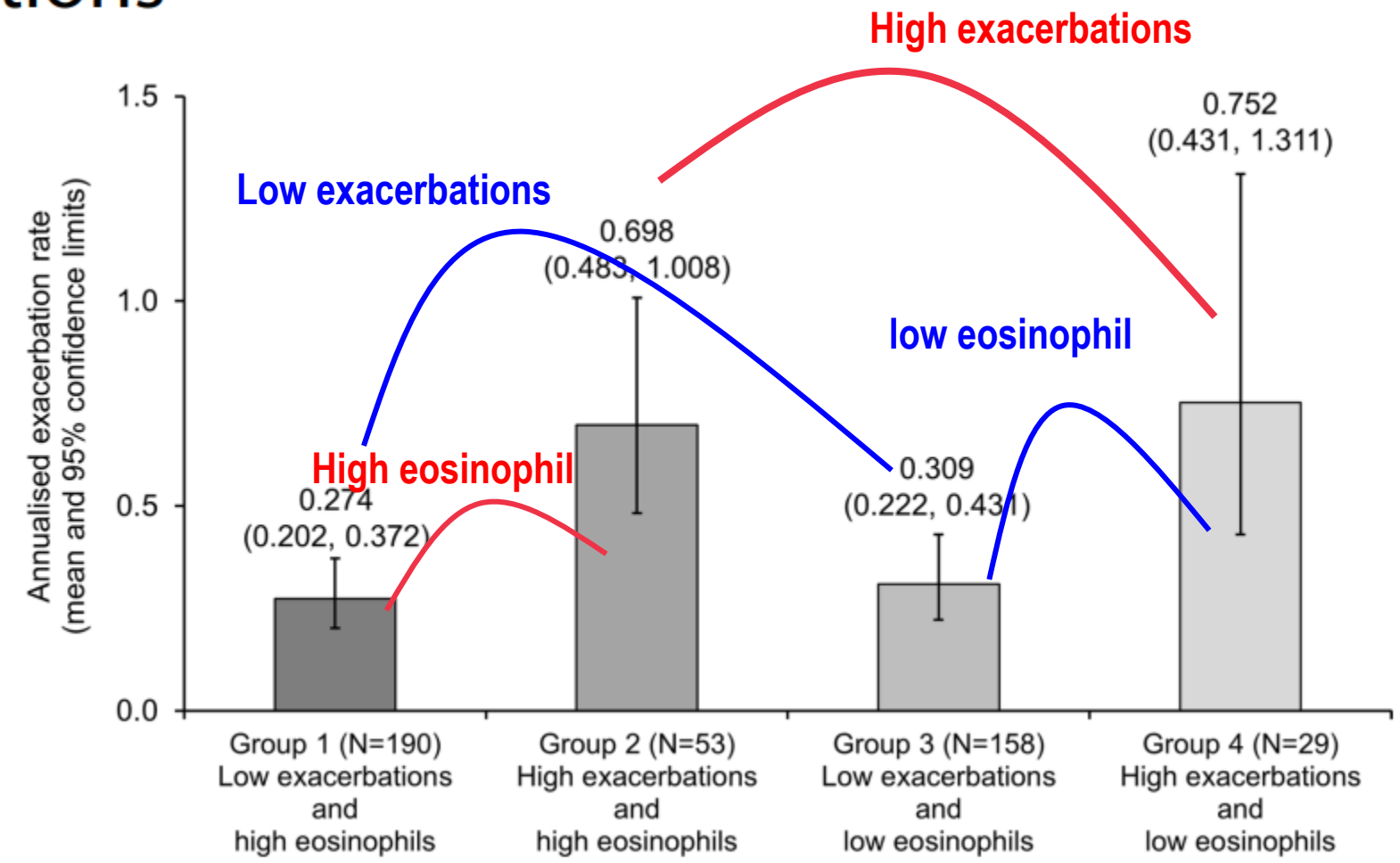


European Respiratory Society guideline. *Eur Respir J.* 2020;55:2000351.

In 'real world' patients with COPD, exacerbation history, and not blood eosinophils, is the most reliable predictor of future exacerbations

LABA/LAMA = 113

Triple therapy = 317



Worth et al. Respiratory Research (2023) 24:2

SITT VS Dual Bronchodilator Therapy in COPD: Real-World Comparative Effectiveness and Safety -Samy Suissa-

United Kingdom's Clinical Practice Research Datalink
real-world practice setting
ICS-naïve patients (Adaptive selection design)

- 4106 of SITT and 29,702 of dual bronchodilators

Adjusted Hazard Ratios of a Moderate or Severe COPD Exacerbation

	Number of Patients	Number with Events	Person-Years	Rate* Per 100 Per Year	Rate† Per 100 Per Year	Adjusted† HR (95% CI)
Overall						
Triple therapy	4106	1304	1494	86.6	64.8	1.08 (1.00–1.16)
Dual bronchodilator	29,702	7030	12,344	56.1	59.1	1.00 (Reference)
COPD exacerbations in prior year						
None						
Triple therapy	1754	271	731	37.2	34.8	1.19 (1.02–1.39)
Dual bronchodilator	18,738	2435	8551	28.5	28.7	1.00 (Reference)
One						
Triple therapy	1222	430	434	98.7	98.4	1.17 (1.04–1.32)
Dual bronchodilator	6731	2174	2620	82.1		
Two or more						0.83 (0.74–0.92)
Triple therapy	1130	603	330	182.9		
Dual bronchodilator	4233	2421	1174	206.2		1.00 (Reference)
Prior asthma diagnosis						
None						
Triple therapy	3553	1129	1296	86.4	65.2	1.10 (1.01–1.19)
Dual bronchodilator	27,630	6493	11,534	55.5	58.1	1.00 (Reference)
Yes						
Triple therapy	553	175	198	88.1	62.3	0.86 (0.70–1.06)
Dual bronchodilator	2072	537	810	66.1	72.9	1.00 (Reference)
Baseline blood eosinophil count (cells/μL)						
< 150						
Triple therapy	1191	382	412	92.2	67.6	1.12 (0.98–1.29)
Dual bronchodilator	9445	2201	3921	55.6	58.6	1.00 (Reference)
150–300						
Triple therapy	1501	472	539	86.6	67.2	1.13 (0.99–1.28)
Dual bronchodilator	11,285	2644	4722	54.9	57.5	1.00 (Reference)
>300						
Triple therapy	799	274	305	88.4	62.5	0.89 (0.76–1.05)
Dual bronchodilator	4764	1314	1900	68.1	71.9	1.00 (Reference)

International Journal of Chronic Obstructive Pulmonary Disease 2022:17 1975–1986

SITT VS Dual Bronchodilator Therapy in COPD: Real-World Comparative Effectiveness and Safety

-Samy Suissa-

	Number of Patients	Number with Events	Person-Years	Rate* Per 100 Per Year	Rate† Per 100 Per Year	Adjusted† HR (95% CI)
Moderate or severe exacerbation						
Triple therapy	4106	1304	1494	86.6	64.8	1.08 (1.00–1.16)
Dual bronchodilator	29,702	7030	12,344	56.1	59.1	1.00 (Reference)
Severe exacerbation						
Triple therapy	4106	283	1961	14.4	10.1	1.32 (1.13–1.55)
Dual bronchodilator	29,702	1029	14,739	7.0	7.6	1.00 (Reference)
All-cause mortality						
Triple therapy	4106	275	2034	13.3	9.6	1.53 (1.30–1.79)
Dual bronchodilator	29,702	900	14,970	6.0	6.3	1.00 (Reference)
Severe pneumonia						
Triple therapy	4106	317	1966	15.9	11.7	1.50 (1.29–1.75)
Dual bronchodilator	29,702	1079	14,740	7.3	7.8	1.00 (Reference)

Notes: *Crude, computed before weighing by fine stratification of propensity scores. † After weighting by fine stratification weights from the probability of treatment propensity scores, stratified by prior use of LAMA or LABA.

..non-recommended patterns of triple therapy prescribing in this real-world clinical practice setting

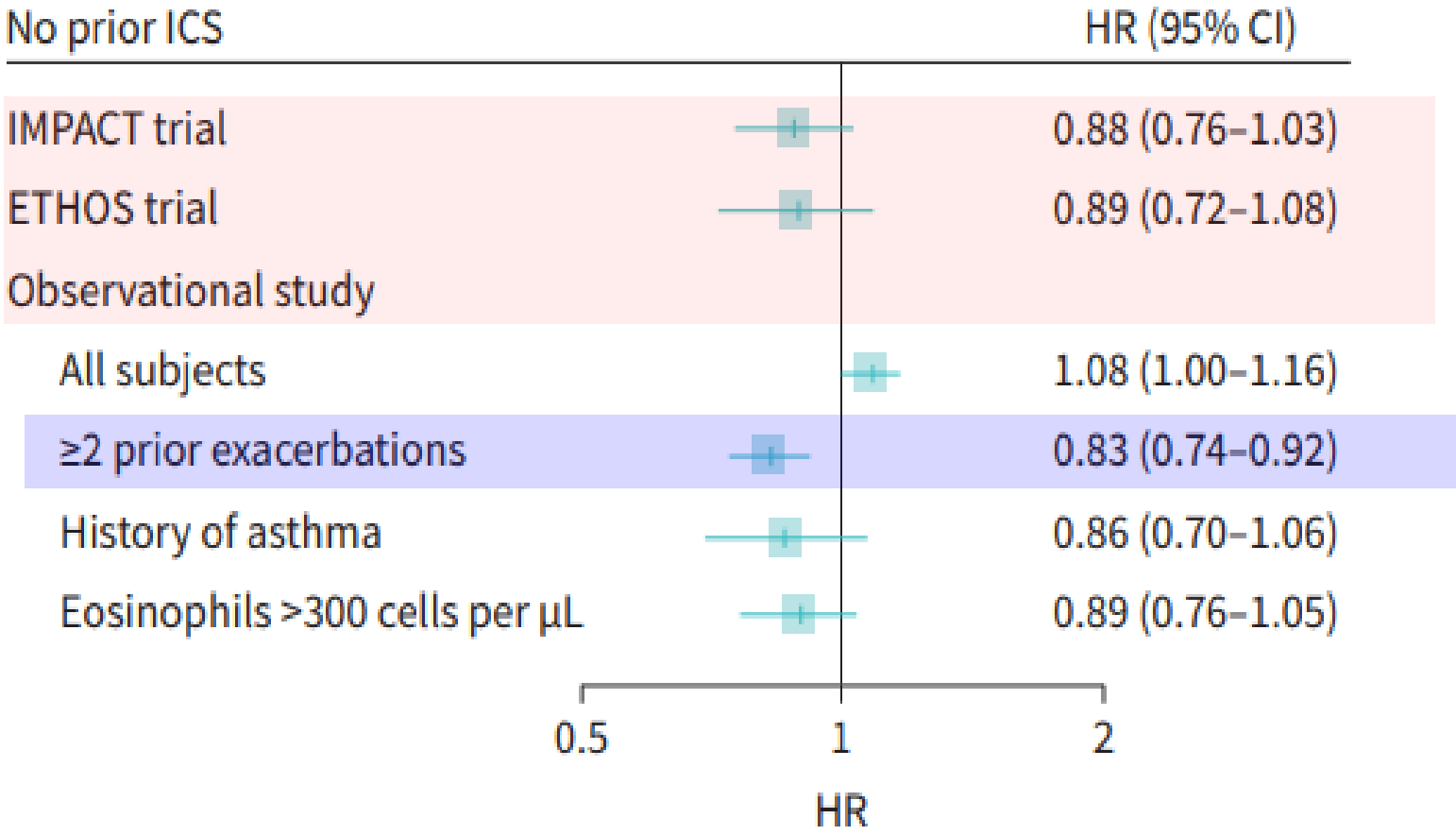
International Journal of Chronic Obstructive Pulmonary Disease 2022:17 1975–1986

Triple therapy in COPD: understanding the data

Samy Suissa [1,2]

Hazard ratio (HR) of a **moderate or severe COPD exacerbation**, triple vs dual

ICS-naïve patients over **3,000 pts**
1,700 pts



ERJ Open Res 2023; 9: 00615-2022

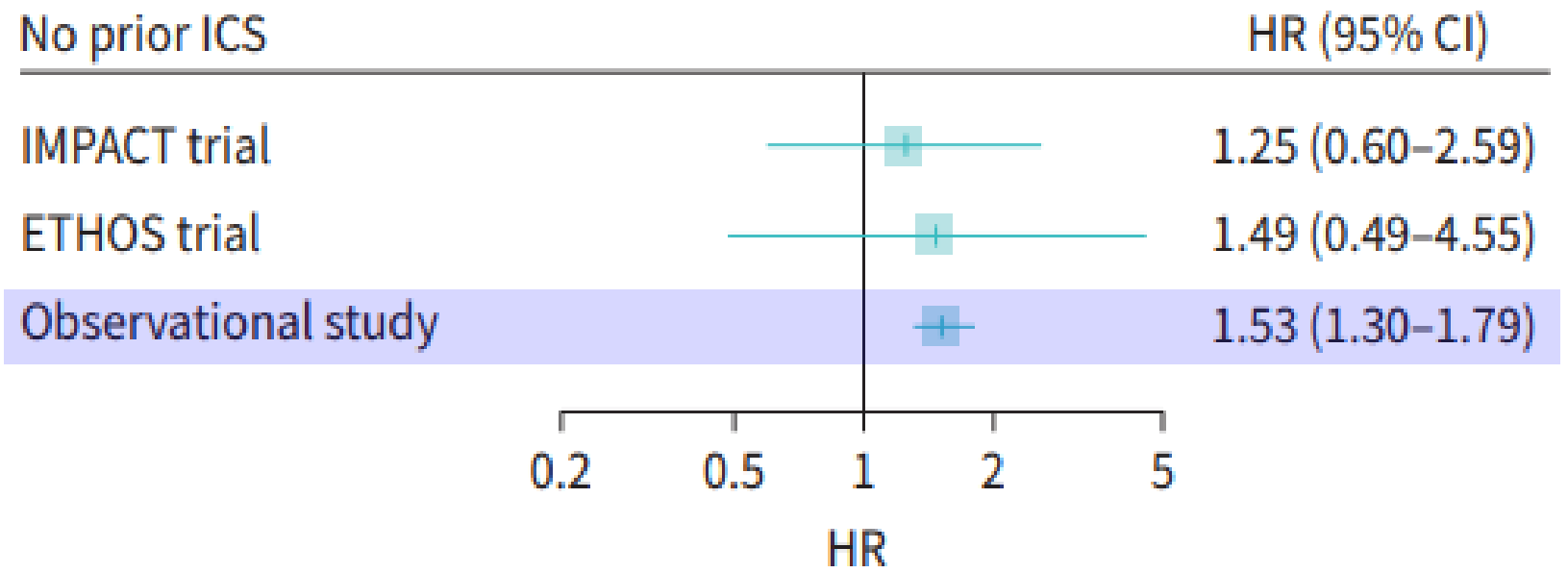
Triple therapy in COPD: understanding the data

Samy Suissa [1,2]

Hazard ratio (HR) of **all-cause mortality**, triple vs dual

ICS-naïve patients over **3,000 pts**

1,700 pts



ERJ Open Res 2023; 9: 00615-2022

Contents

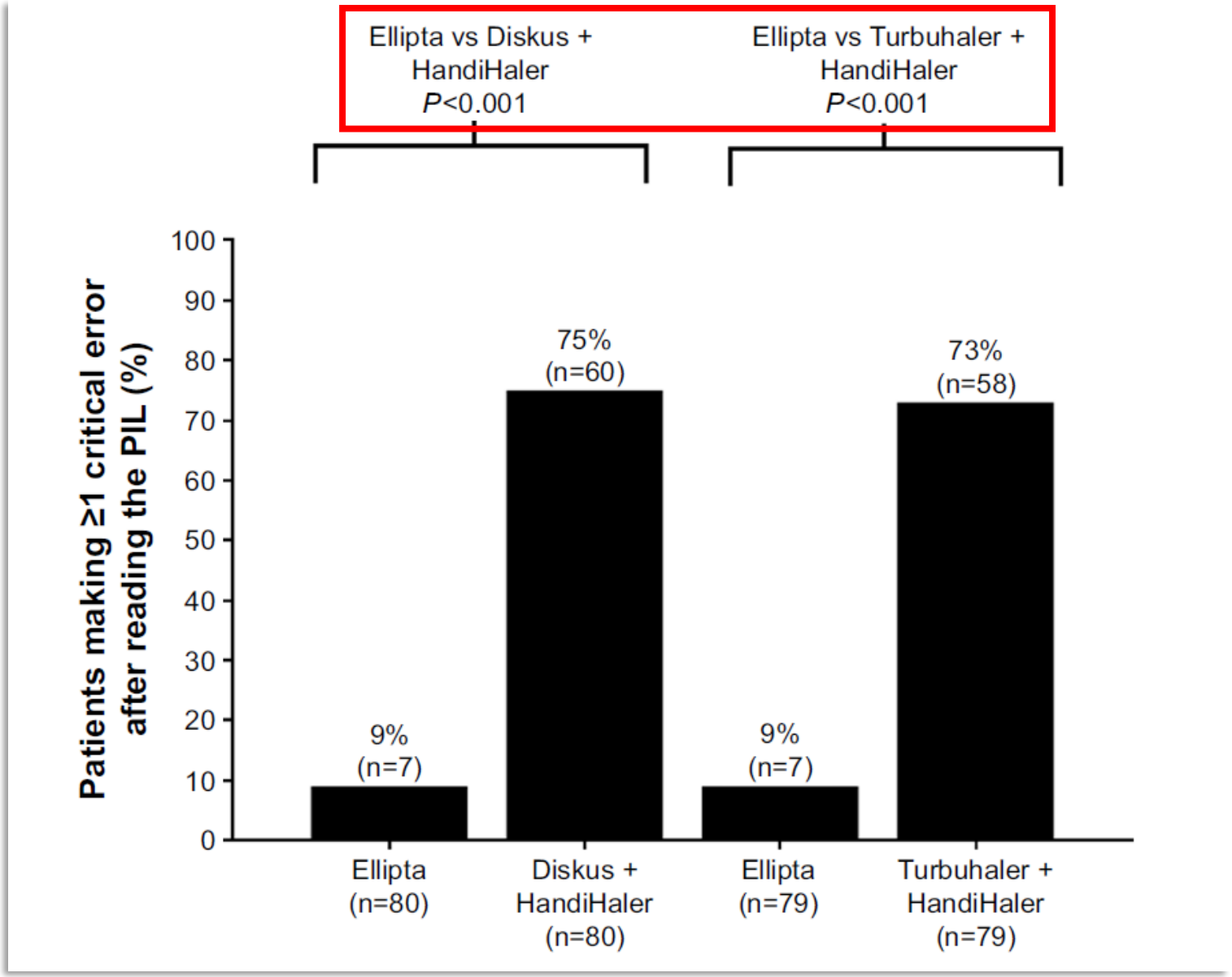
- The evidence of Triple therapy in RCT study
- Real world evidence
- **The issue of Device**

A randomized, open-label, single-visit, crossover study simulating triple-drug delivery with Ellipta compared with dual inhaler combinations in patients with COPD

Single vs multiple devices

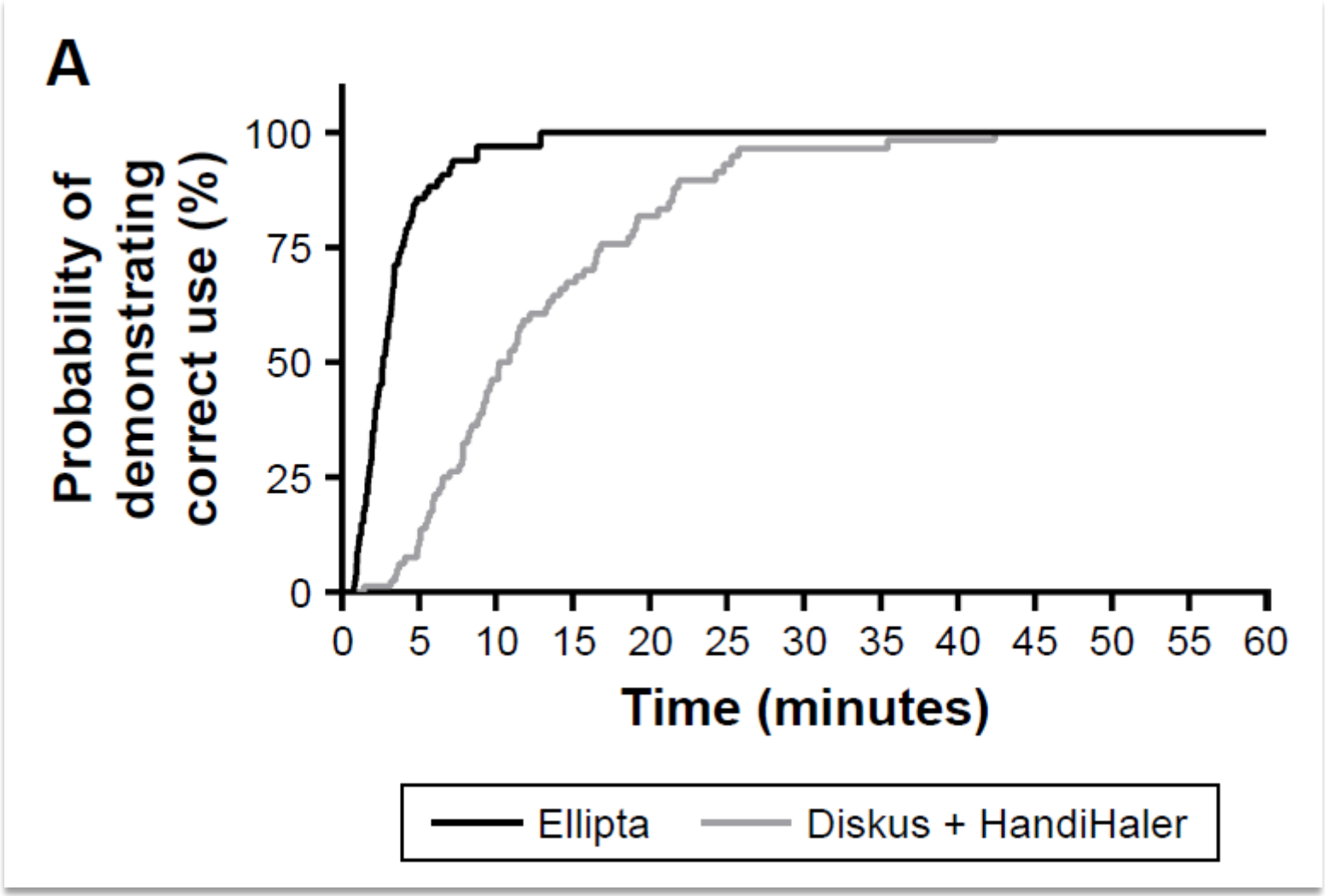
van der Palen J;International journal of chronic obstructive pulmonary disease;2018;13;2515-2523

Proportion of patients with at least one critical error



van der Palen J;International journal of chronic obstructive pulmonary disease;2018;13;2515-2523

Kaplan-Meier plot of total time taken to demonstrate correct inhaler use



van der Palen J;International journal of chronic obstructive pulmonary disease;2018;13;2515-2523

Adherence and persistence to once-daily single-inhaler versus multiple-inhaler triple therapy among patients with chronic obstructive pulmonary disease in the USA: A real-world study

David Mannino, Michael Bogart, Benjamin Wu, Guillaume Germain, François Laliberté, Sean D. MacKnight, Young Jung, Marjorie Stiegler, Mei Sheng Duh

Methods: This retrospective analysis of the IQVIA PharMetrics Plus claims database

identified patients with COPD initiating triple therapy between 18/09/2017 and 30/06/2019.

Single vs multiple devices

To appear in: *Respiratory Medicine*

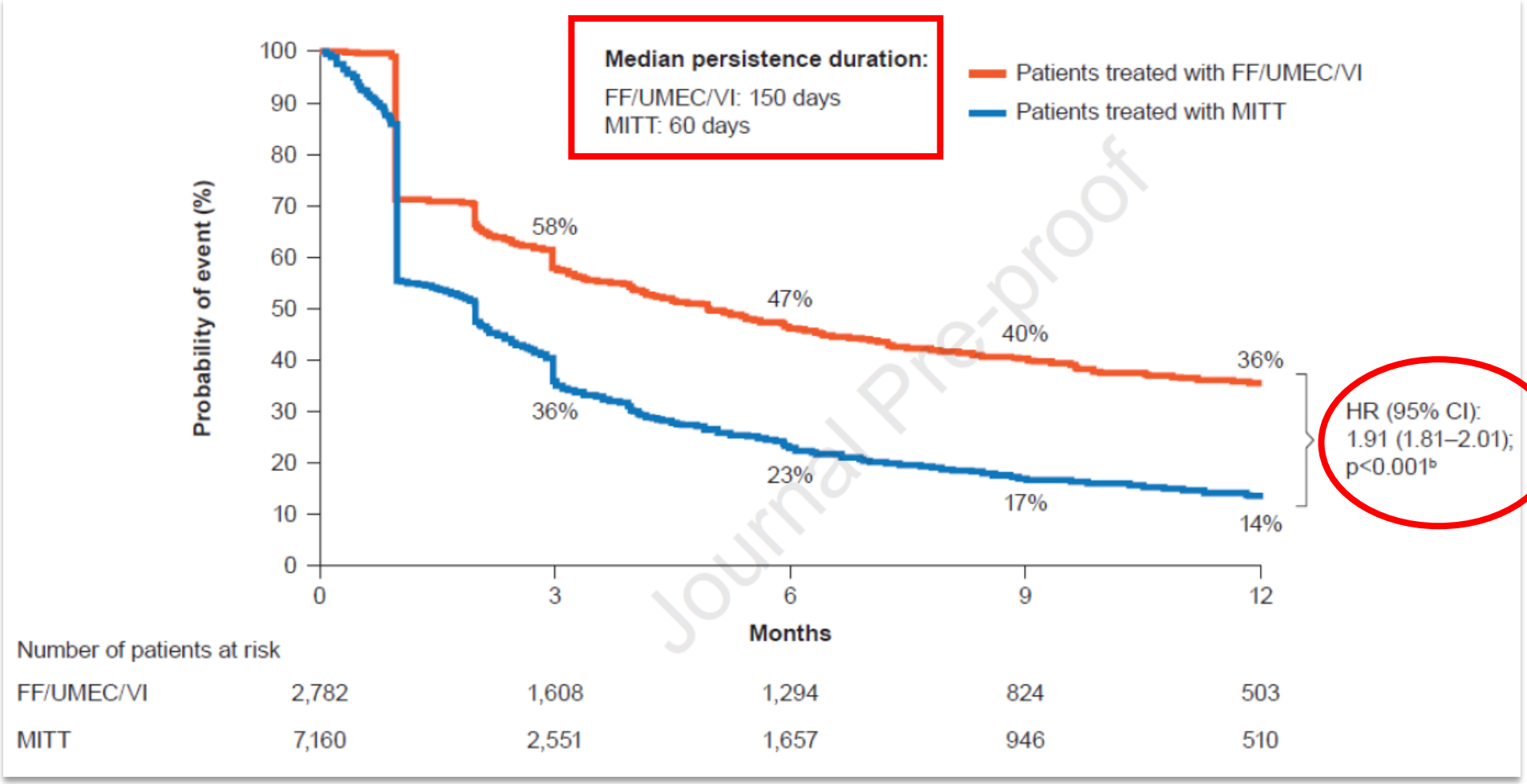
Received Date: 24 September 2021

Revised Date: 23 February 2022

Accepted Date: 6 March 2022

David Mannino et al, Respiratory Medicine;2022; DOI: https://doi.org/10.1016/j.rmed.2022.106807

Kaplan-Meier persistence rates for the weighted FF/UMEC/VI and MITT cohorts (non-persistence defined as a gap of >30 days[a]).



David Mannino et al, Respiratory Medicine;2022; DOI: https://doi.org/10.1016/j.rmed.2022.106807

Summary

- Single-inhaler triple therapy reduced the **risk of moderate/severe hospitalised exacerbations,** improved **lung function, TDI, QoL** compared with dual therapies (LAMA/LABA and ICS/LABA)
- Single-inhaler triple therapy **reduced the risk of ACM** versus LABA/LAMA **(IMPACT, ETHOS)**
- Real world evidence with triple therapy showed the improvement of **PFT, QOL and Exacerbation,** should be initiated mainly in **patients with multiple exacerbations**
- In a usual clinical care setting, treatment with once-daily single-inhaler FF/UMEC/VI resulted in **health status** improvement and greater **lung function** improvement versus non-ELLIPTA MITT **(INTREPID)**
- COPD patients initiating single-inhaler FF/UMEC/VI had significantly improved **adherence and persistence** compared with MITT

THANK YOU FOR YOUR ATTENTION !