ICS as a first combination option in group D of COPD
: pro

2018. 6. 16.

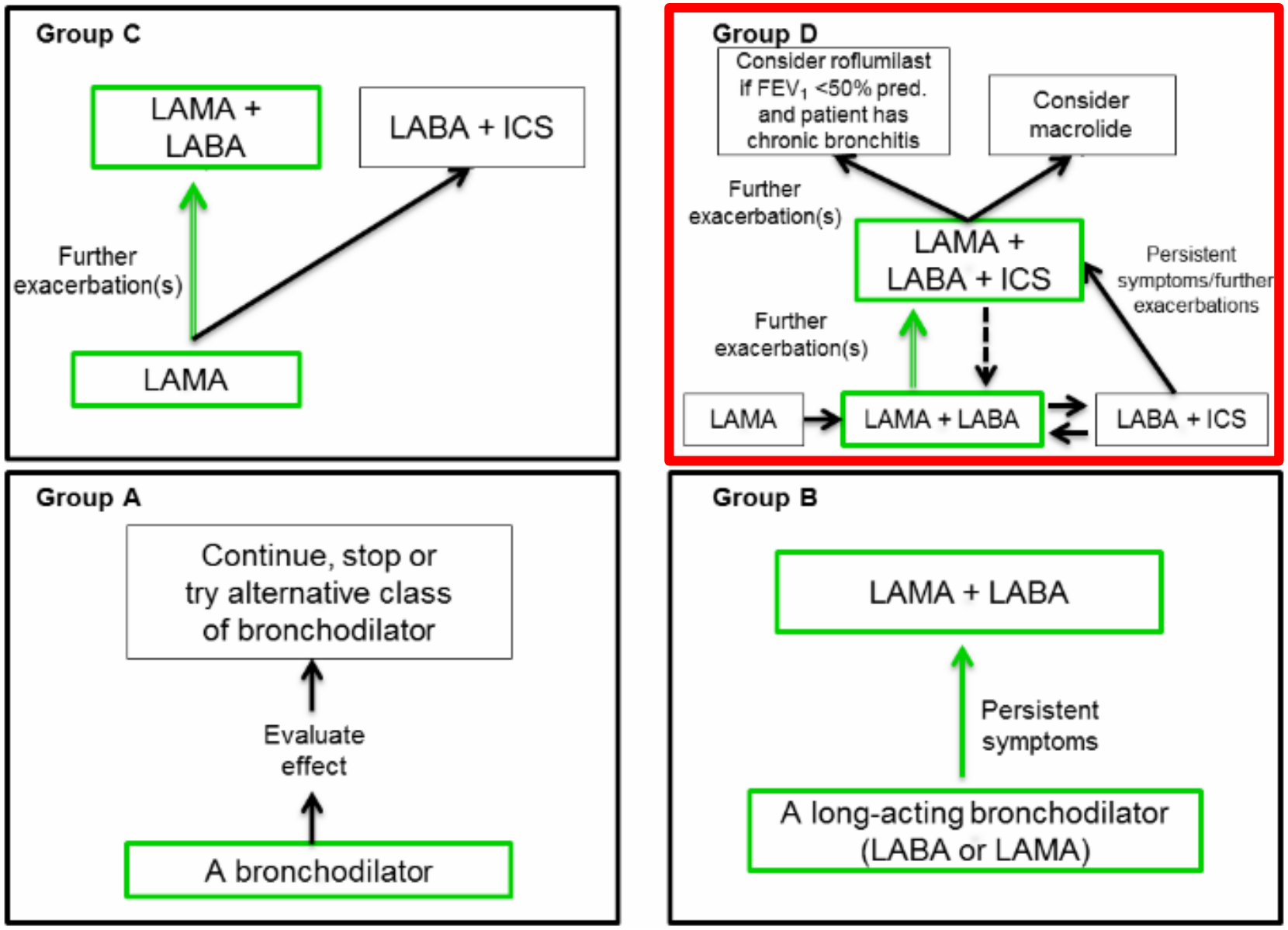
Chang-Hoon Lee

Before GOLD 2017

Group C ICS/LABA or LAMA	**Group D** ICS/LABA and/or LAMA
Group A SABA prn or SAMA prn	**Group B** LABA or LAMA

GOLD update 2016.

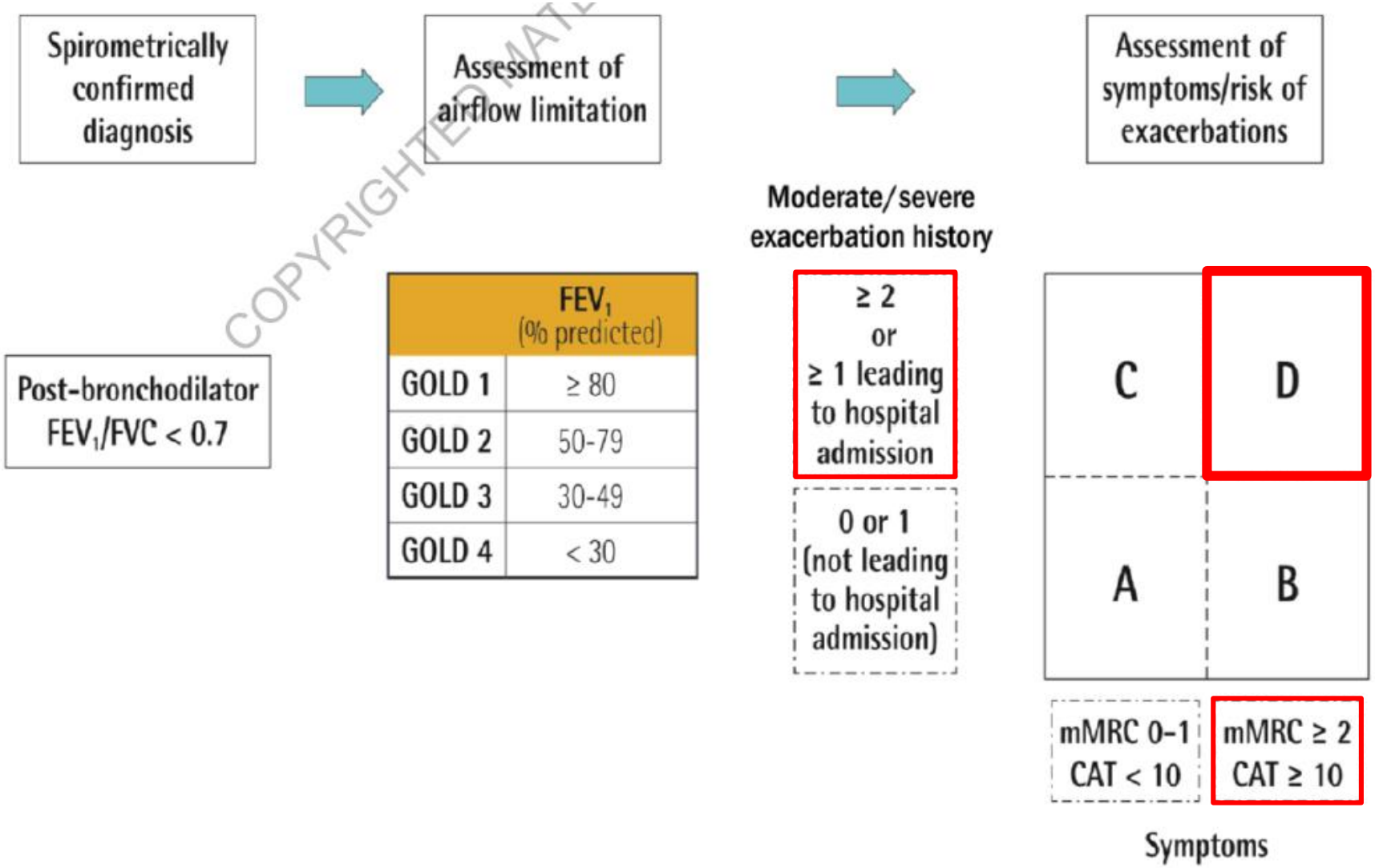
GOLD 2017



: preferred treatment pathways

GOLD update 2018.

COPD groups

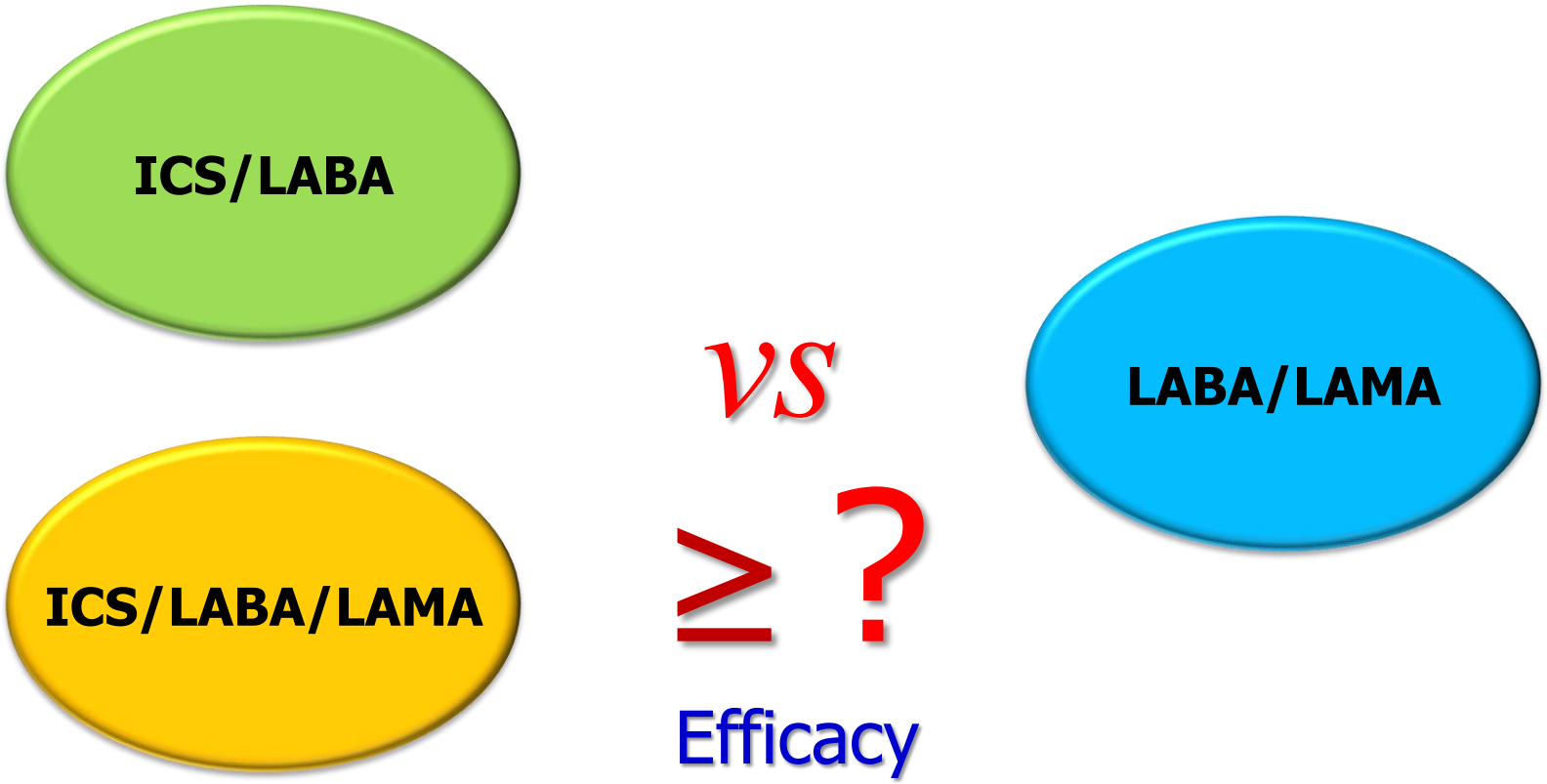


GOLD update 2018.

Abbreviation

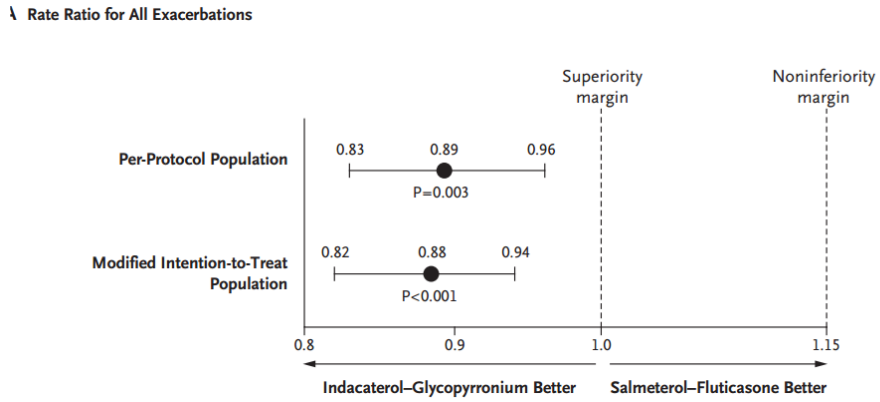
ICS	LABA	LAMA
Beclomethasone dipropionate (BDP) Budesonide (BUD) Fluticasone propionate (FP) Fluticasone furoate (FF)	Formoterol (FOR) Salmeterol (SAL) Indacaterol (IND) Vilanterol (VIL) Olodaterol (OLO)	Tiotropium (TIO) Glycopyrronium (GLY) Aclidinium (ACL) Umeclidinium (UMEC)

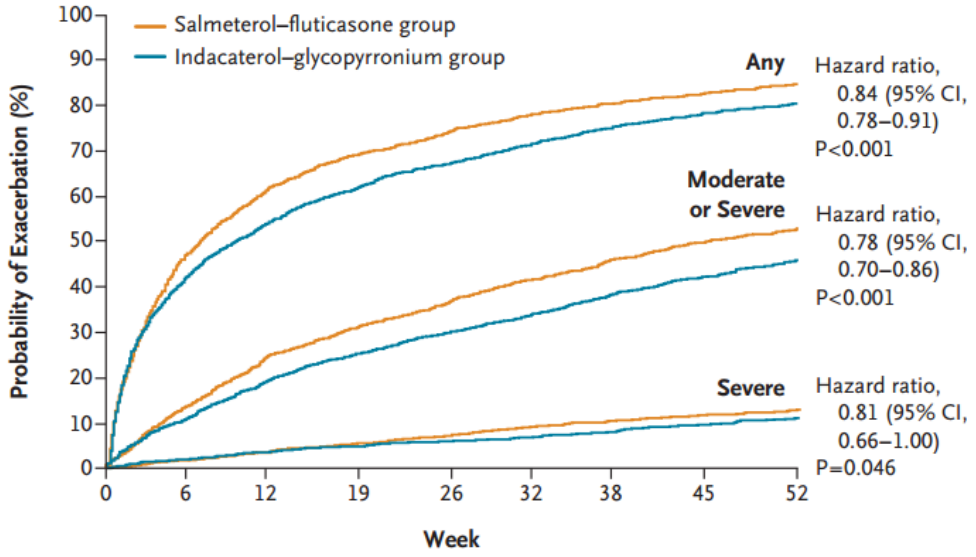
in group D COPD patietns



FP/SAL < IND/GLY : AE

Double-blind RCT (FLAME). COPD pts with FEV1 25-59%, **mMRC ≥ 2, AE ≥ 1 /yr** (**N=3,362**).
Indacaterol 110 µg/Glycopyrronium 50µg (QVA149) *vs* FP/SAL 500/50µg for **52 weeks**.
Primary endpoint: **all AE (noninferiority)**





Wedzicha JA. N Engl J Med 2016;374:2222.

FP/SAL *vs* IND/GLY : AE in group D

Double-blind RCT (FLAME). COPD pts with FEV1 25-59%, **mMRC ≥ 2, AE ≥ 1 /yr** (**N=3,362**).
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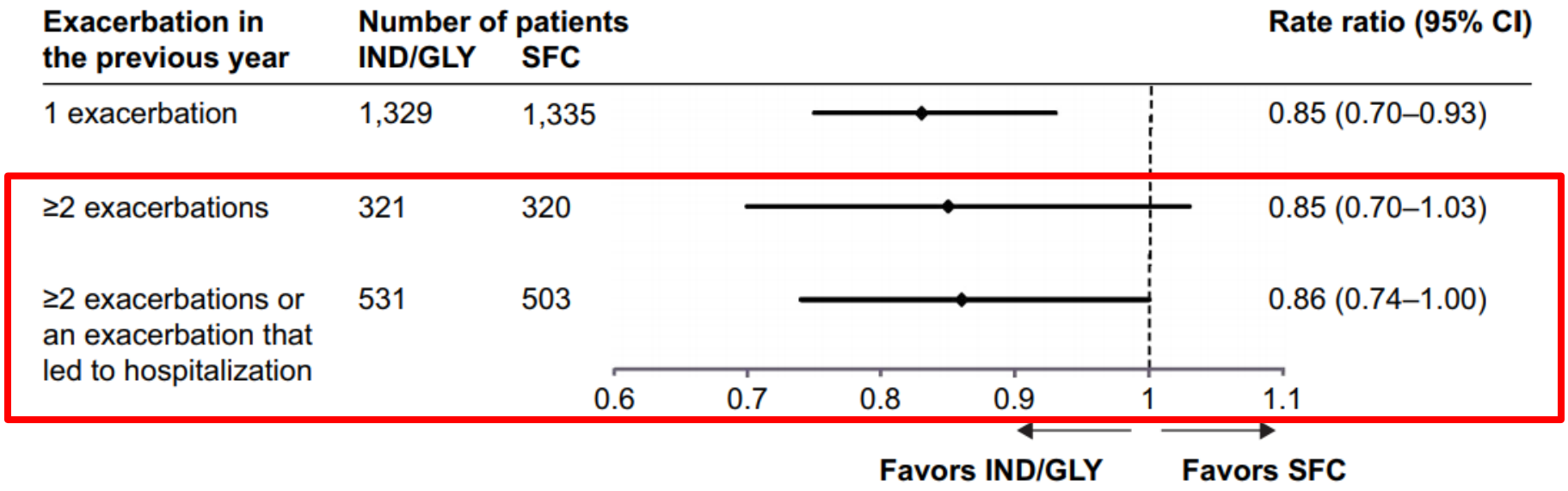
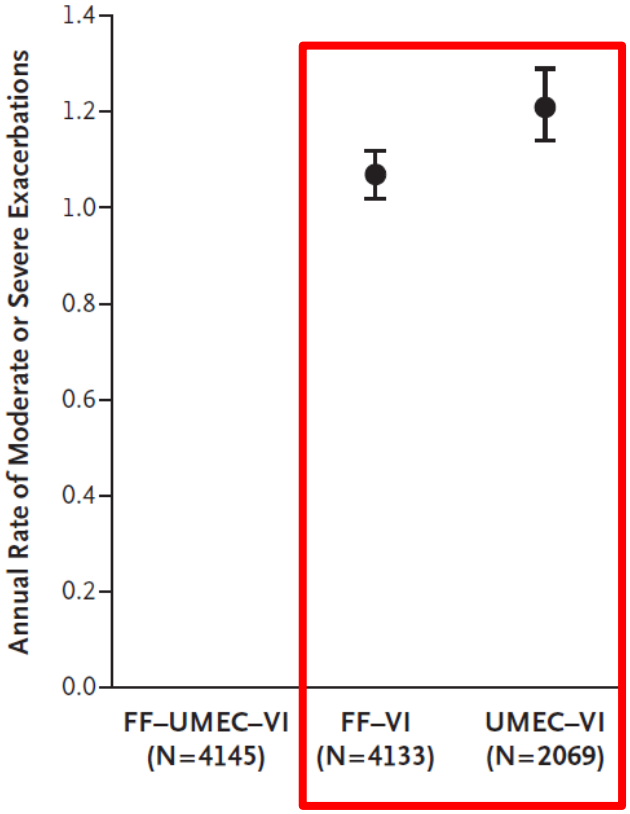
Predefined analysis + Post hoc analysis



Vogelmeier C. Int J Chron Obstruct Pulmon Dis 2018;13:1125.

FF/VI *vs* VIL/UMEC : AE

Double-blind RCT (IMPACT). COPD pts FEV1<50%+**AE≥1/yr** or 50-80%+**AE≥2 /yr** (**CAT 20.1±6.1**)
FF/VI/UMEC 100/25/62.5μg *vs* FF/VI *vs* UMEC/VIL for **52 weeks**. (**N=4,151+4,134+2,070**).
Primary endpoint: moderate-to-severe AE rate



Moderate-to-severe exacerbation rate

[1] FF/VI/UMEC group: 0.91 per year

[2] FF/VI group: 1.07 per year

[3] UMEC/VI group: 1.21 per year

1 *vs* 2: P<0.001

1 *vs* 3: P<0.001

2 *vs* 3: P<0.05

Lipson DA. N Engl J Med 2018 (Epub).

FF/VI *vs* VIL/UMEC : AE in group D

Double-blind RCT (IMPACT). COPD pts FEV1<50%+**AE≥1/yr** or 50-80%+**AE≥2 /yr** (**CAT 20.1±6.1**)
FF/VI/UMEC 100/25/62.5µg *vs* FF/VI *vs* UMEC/VIL for **52 weeks**. (**N=4,151+4,134+2,070**).
Primary endpoint: moderate-to-severe AE rate

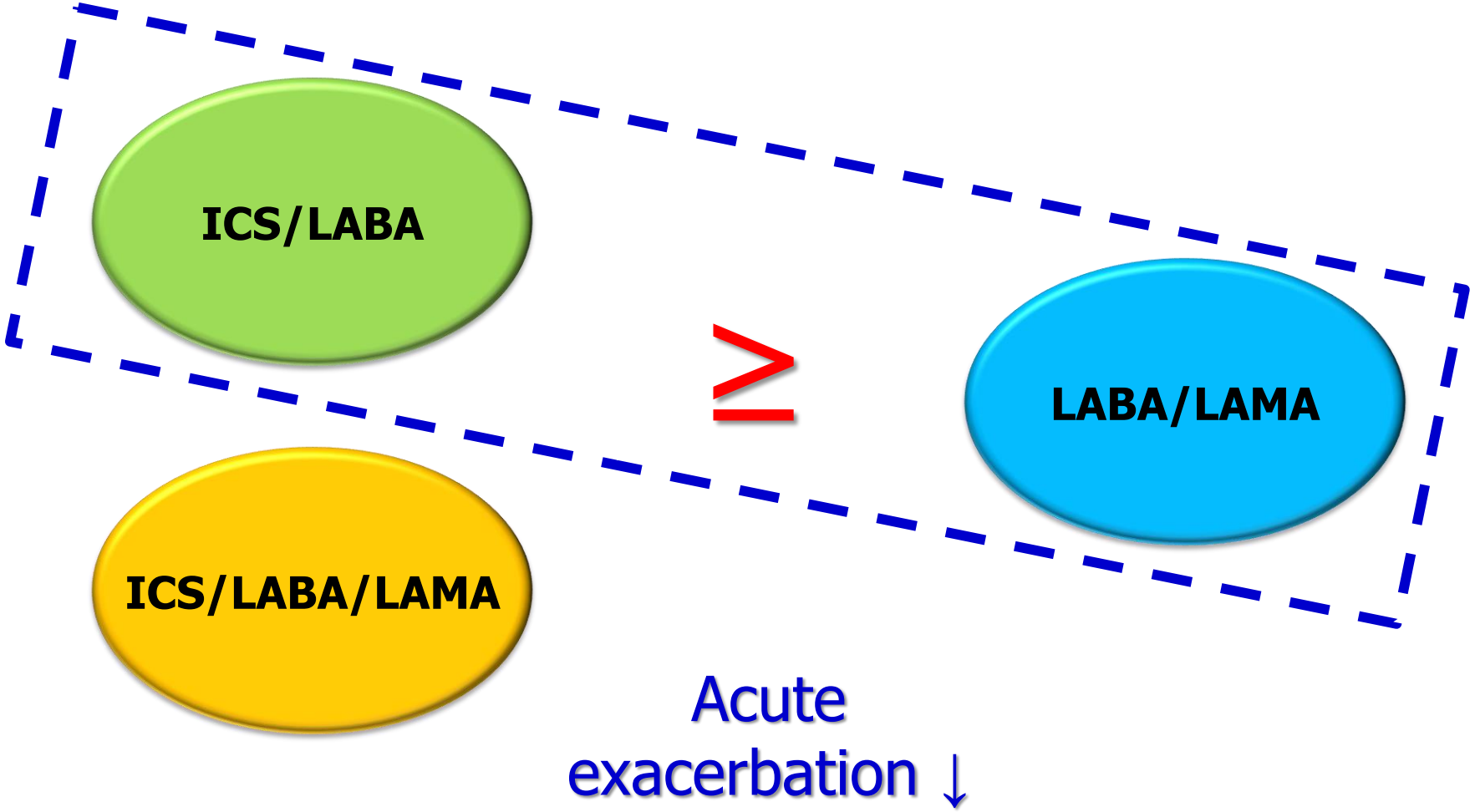
Prespecified analysis

	FF/VI	UMEC/VI
Total	1.07 (1.02-1.12)	1.21 (1.14-1.29)
AE ≤ 1 in the past year	1.08 (1.01-1.15)	1.08 (0.98-1.19)
AE ≥ 2 in the past year	1.06 (1.00-1.12)	1.32 (1.21-1.43)

-25% (95% CI, -13 to -38) *P*<0.001

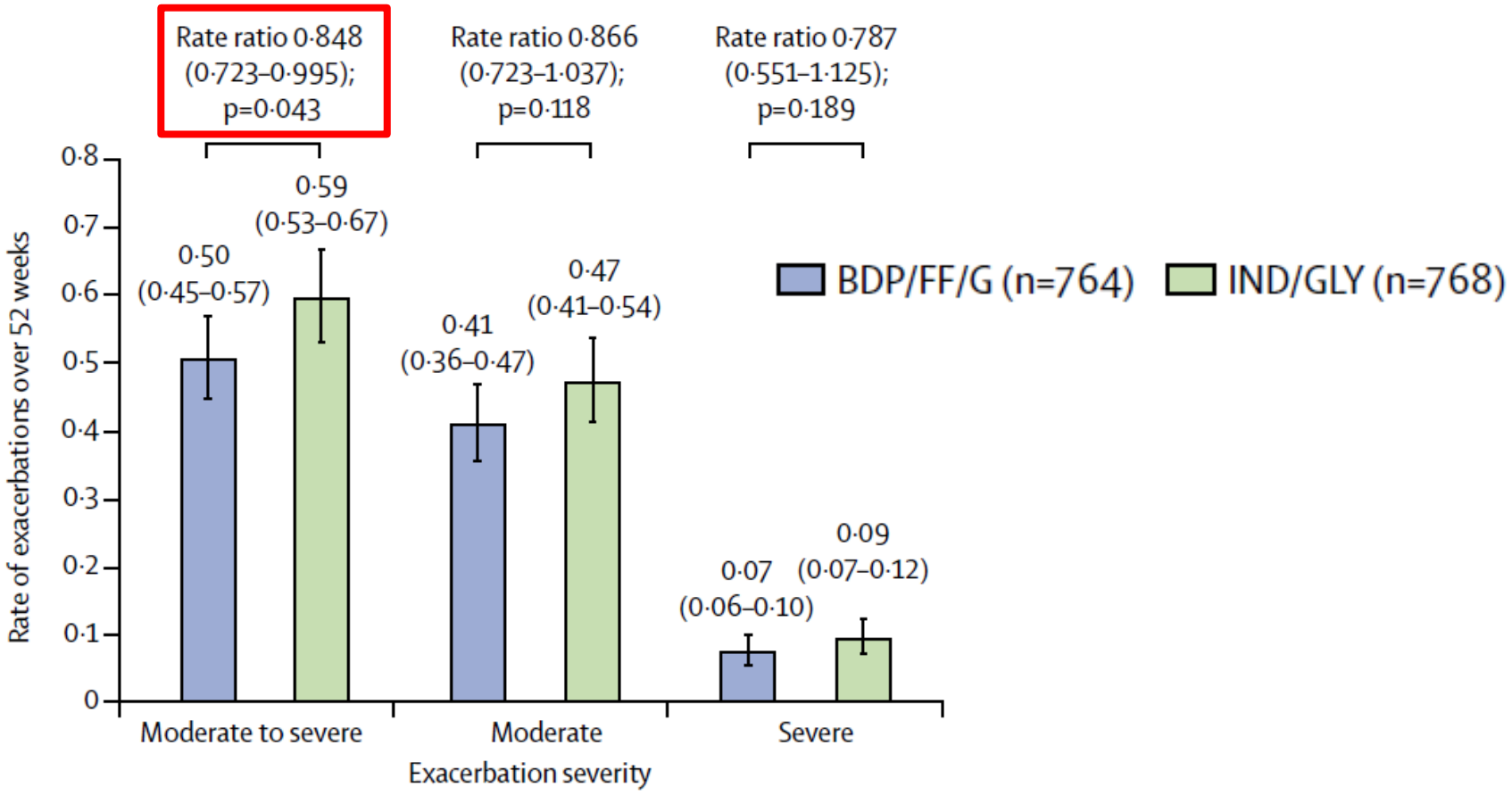
Lipson DA. N Engl J Med 2018 (Epub).
+ data by courtesy of GSK.

in group D COPD patietns



BDP/FOR/GLY *vs* IND/GLY: AE

Double-blind RCT (TRIBUTE). COPD pts with FEV1<50%+**AE≥1 /yr**. (**N=1,532**)
BDP/FOR/GLY 87/5/9µg bid *vs* IND/GLY 85/43 µg for **52 weeks**.
Primary endpoint: **moderate-to-severe AE rate**



Papi A. Lancet 2018;391:1076.

BDP/FOR/GLY *vs* IND/GLY: AE in group D

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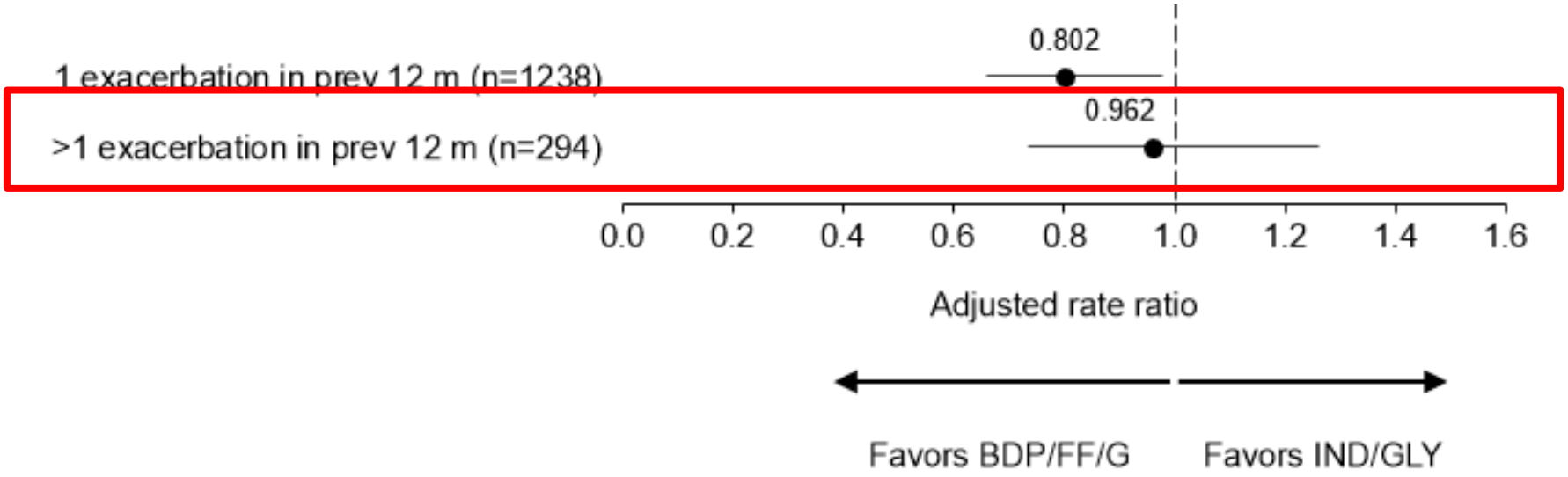
Primary endpoint: **moderate-to-severe AE rate**

Prespecified subgroup analysis



Papi A. Lancet 2018;391:1076.

FF/VI/UMEC *vs* UMEC/VI : AE

Double-blind RCT (IMPACT). COPD pts FEV1<50%+**AE≥1/yr** or 50-80%+**AE≥2 /yr** (**CAT 20.1±6.1**)
FF/VI/UMEC 100/25/62.5μg *vs* FF/VI *vs* UMEC/VIL for **52 weeks**. (**N=4,151+4,134+2,070**).
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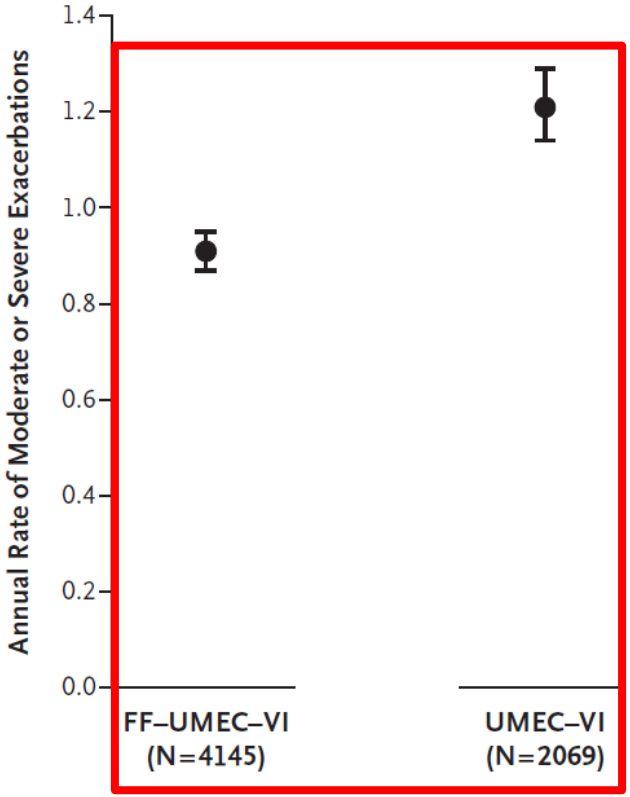

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1 *vs* 2: *P*<0.001
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Lipson DA. N Engl J Med 2018 (Epub).

FF/VI/UMEC *vs* VIL/UMEC : AE in group D

Double-blind RCT (IMPACT). COPD pts FEV1<50%+**AE≥1/yr** or 50-80%+**AE≥2 /yr** (**CAT 20.1±6.1**)
FF/VI/UMEC 100/25/62.5µg *vs* FF/VI *vs* UMEC/VIL for **52 weeks**. (**N=4,151+4,134+2,070**).
Primary endpoint: moderate-to-severe AE rate

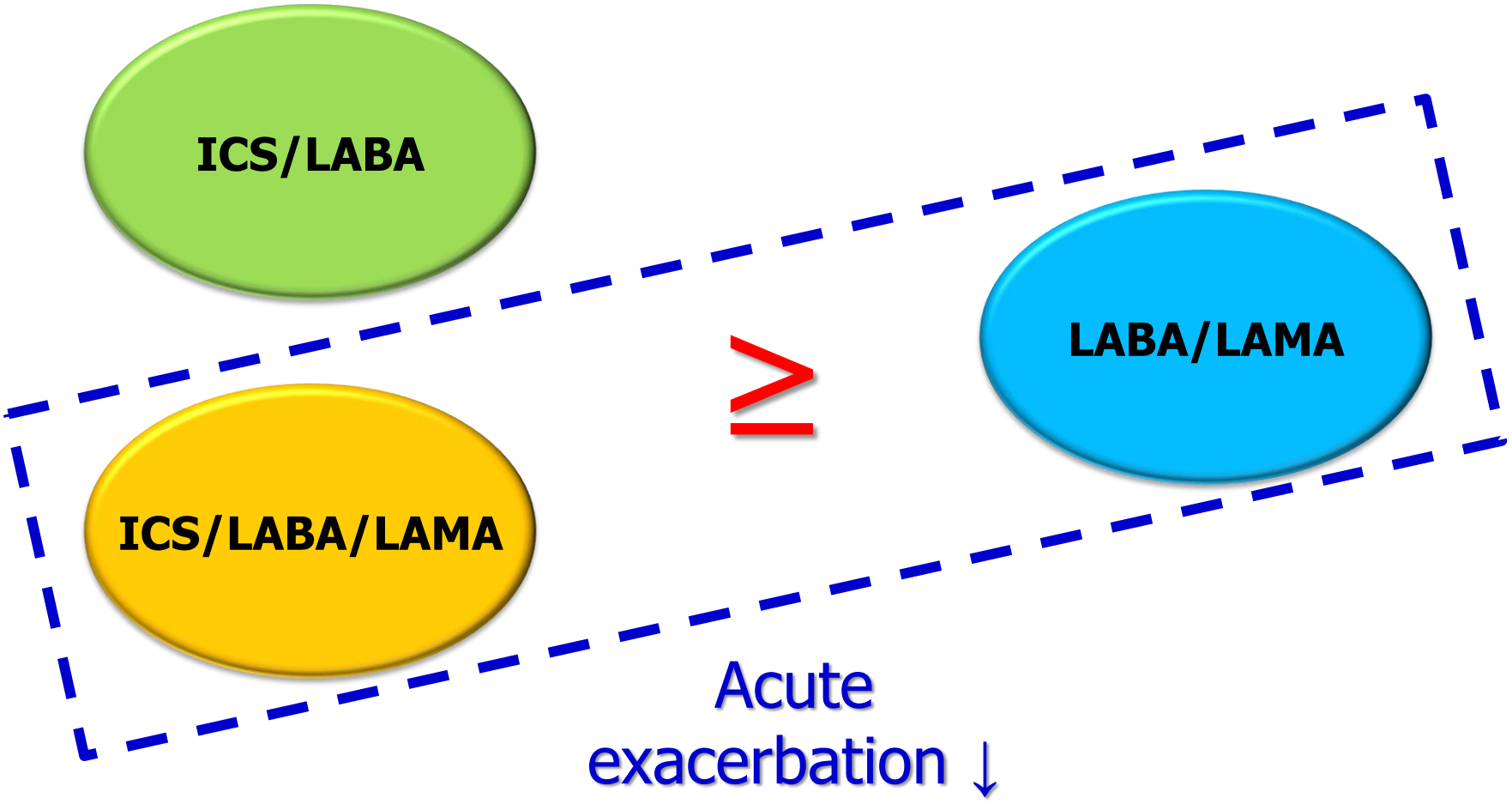
Prespecified subgroup analysis

	FF/VI/UMEC	UMEC/VI
Total	0.91 (0.87-0.95)	1.21 (1.14-1.29)
AE ≤ 1 in the past year	0.86 (0.80-0.92)	1.08 (0.98-1.19)
AE ≥ 2 in the past year	0.94 (0.89-1.00)	1.32 (1.21-1.43)

-28% (95% CI, -21 to -35) *P*<0.001

Lipson DA. N Engl J Med 2018 (Epub).
+ data by courtesy of GSK.

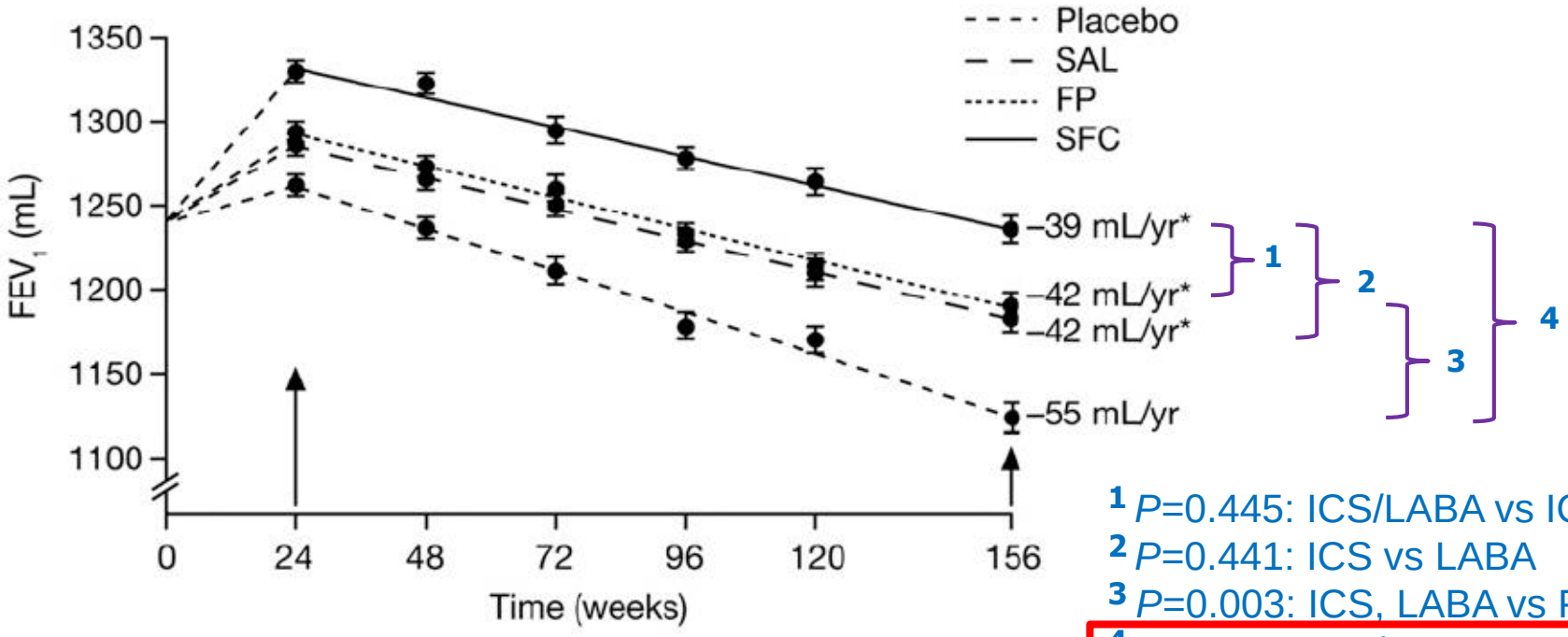
in group D COPD patietns



FP/SAL > PLA : FEV1 decline⇩

Double-blind, multicenter RCT (TORCH).
COPD patients with FEV1<60% (**N=6,184**).
FP (ICS) *vs* SAL (LABA) *vs* FP + SAL (ICS/LABA) vs PLA for **3 years**.
Primary endpoint: **overall mortality.**

Post hoc analysis



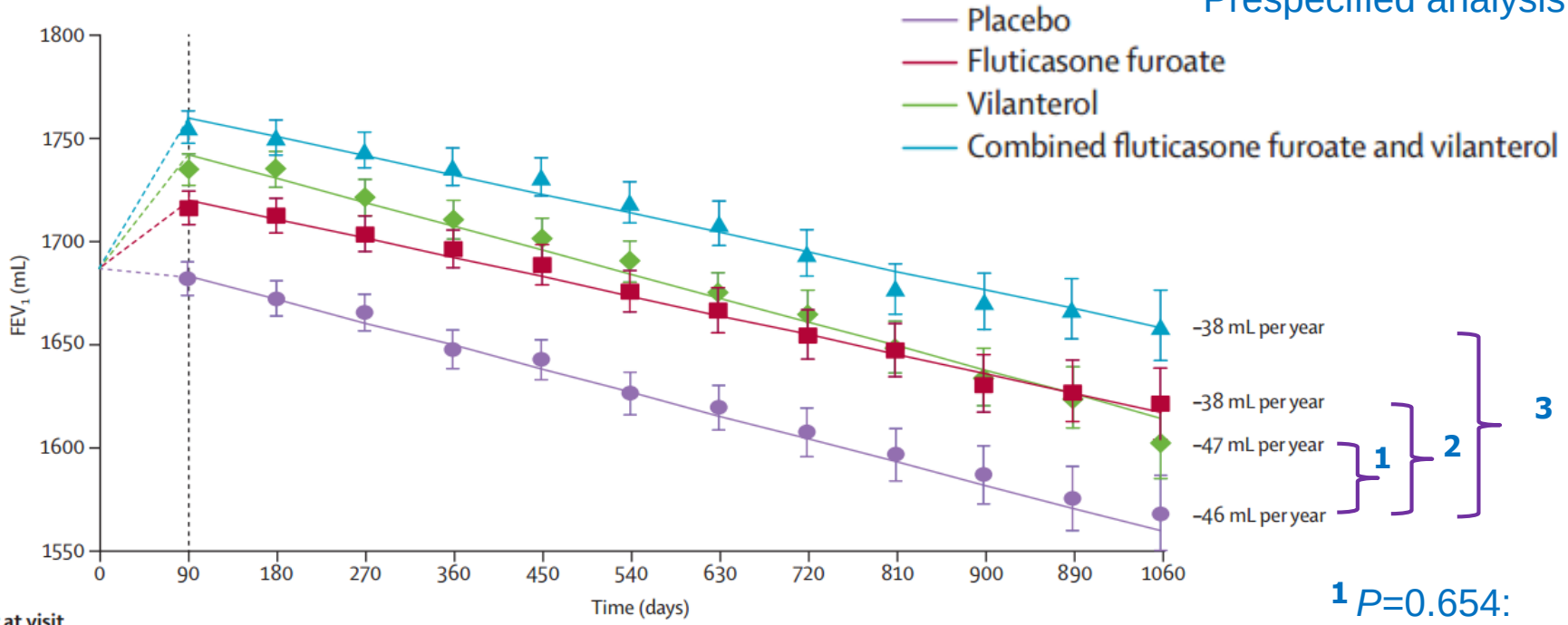
1 *P*=0.445: ICS/LABA vs ICS
2 *P*=0.441: ICS vs LABA
3 *P*=0.003: ICS, LABA vs PLA
4 *P*<0.001: ICS/LABA vs PLA

Celli BR. Am J Respir Crit Care Med 2008:178:332.

FF/VIL > PLA : FEV1 decline⇩

Double-blind, multicenter RCT in 43 countries (SUMMIT). COPD patients with mMRC≥2, FEV1 50-70%, + CV risk (≥60YO+> 2 tx of CAD, PAD, stroke, MI, DM with target organ ds) (**N=16,568**). FF 100 µg qd (ICS) *vs* VIL 25 µg qd (LABA) *vs* FF + VIL (ICS/LABA) *vs* PLA for **3 years**. Primary endpoint: **all-cause mortality**

Prespecified analysis

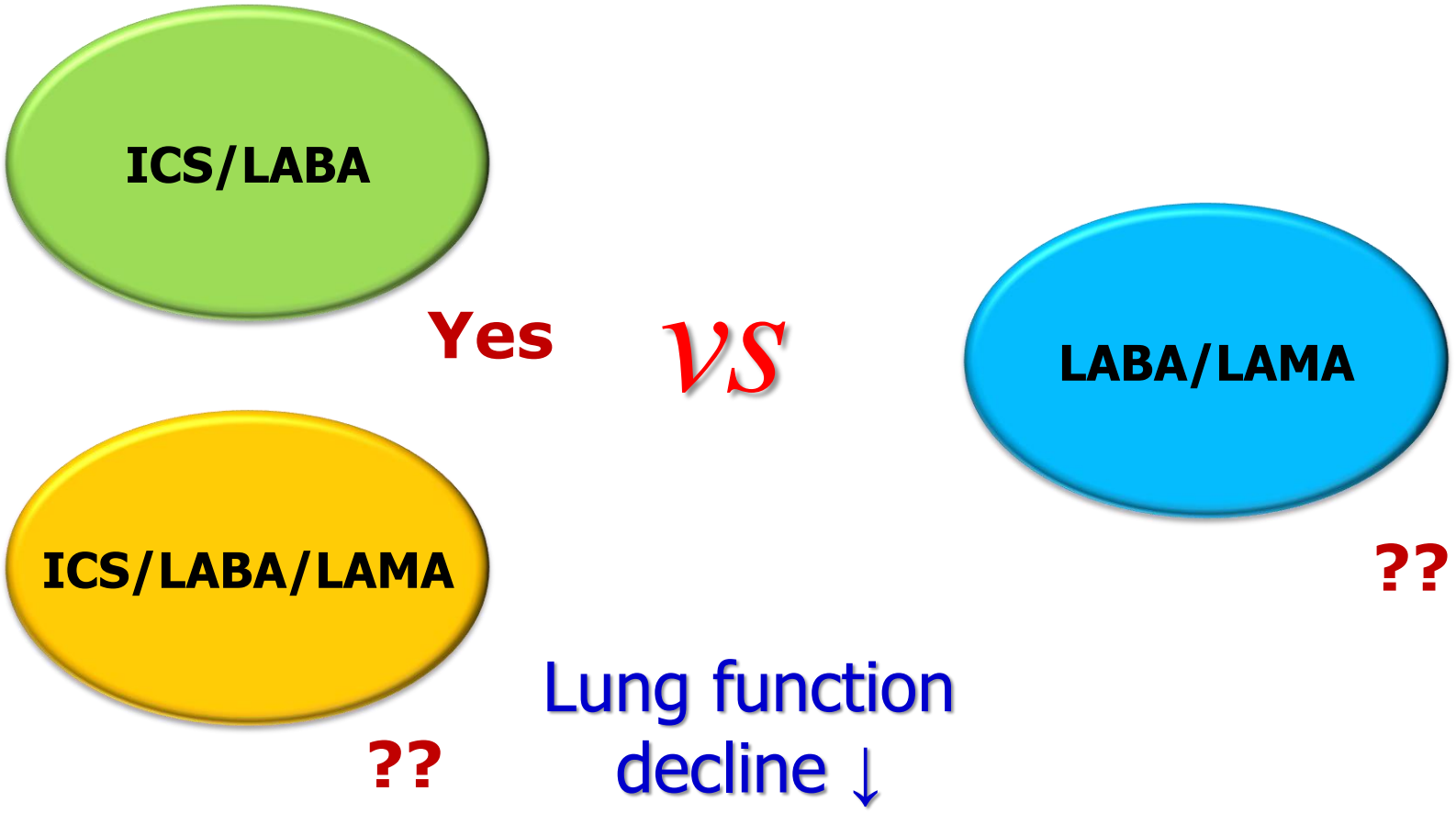


Number at visit													
Placebo	3800	3782	3563	3396	3279	2678	2197	1858	1498	1171	949	736	486
Fluticasone furoate	3879	3858	3688	3580	3452	2777	2311	1936	1569	1246	1001	792	528
Vilanterol	3866	3830	3658	3554	3438	2813	2347	1971	1612	1300	1043	831	542
Combined fluticasone furoate and vilanterol	3912	3883	3731	3610	3505	2864	2391	1997	1633	1290	1035	827	545

1 *P*=0.654:
2 *P*=0.026
3 *P*=0.019

Vestbo J. Lancet 2016;387:1817.

in group D COPD patietns



FF/VI *vs* VIL/UMEC : mortality

Double-blind RCT (IMPACT). COPD pts FEV1<50%+AE≥1/yr or 50-80%+AE≥2 /yr (CAT 20.1±6.1)
FF/VI/UMEC 100/25/62.5µg *vs* **FF/VI** *vs* **UMEC/VIL** for **52 weeks**. (**N=4,151+4,134+2,070**).
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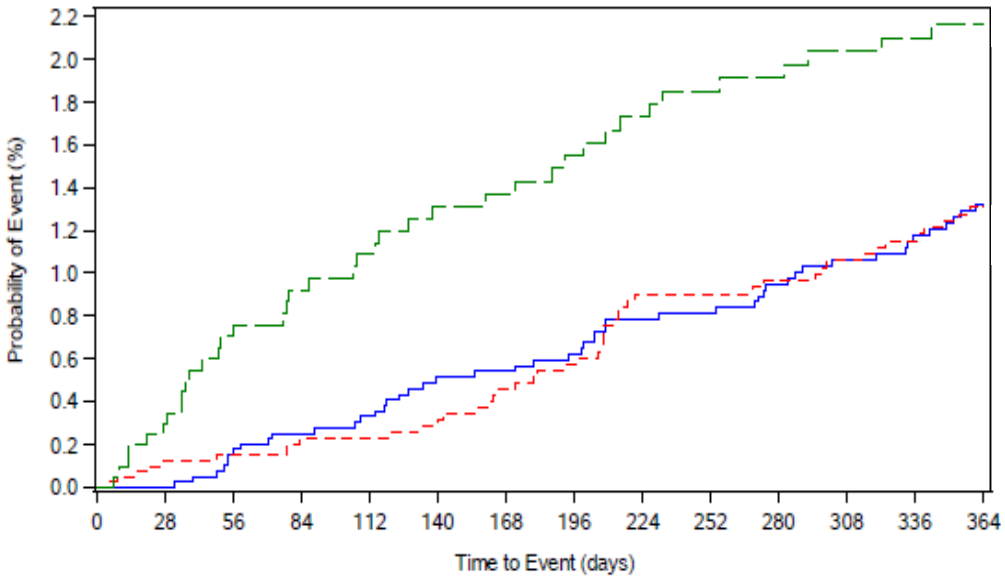

UMEC/VI 62.5/25
FF/VI 100/25
FF/UMEC/VI 100/62.5/25

1 *P*=0.02
2 *P*=0.78
3 *P*=0.01

Lipson DA. N Engl J Med 2018 (Epub).

FP/SAL *vs* IND/GLY : mortality

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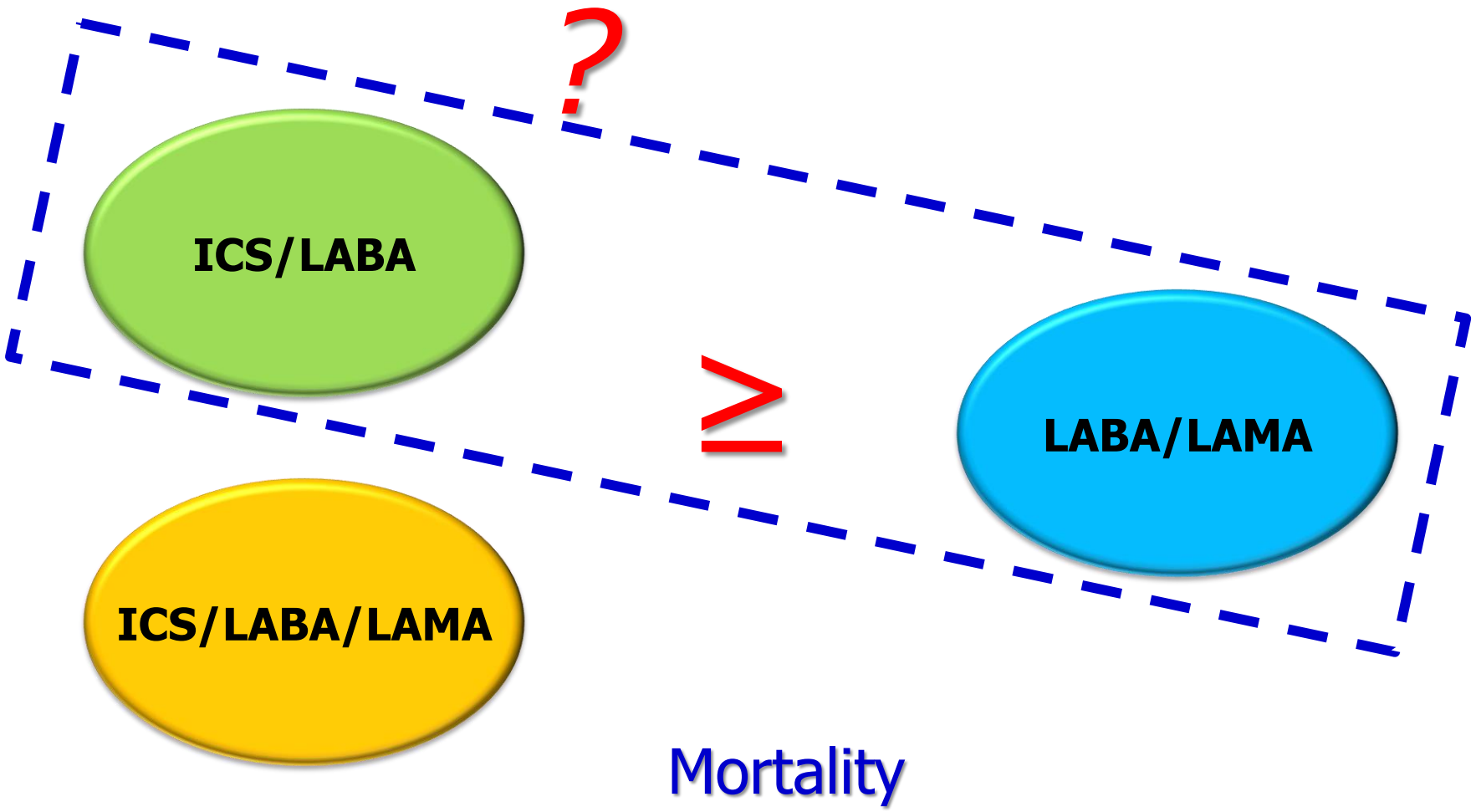
Primary endpoint: **all AE (noninferiority)**

Variable	Indacaterol–Glycopyrronium Group (N=1678)	Salmeterol–Fluticasone Group (N=1680)
	number (percent)	
Death	24 (1.4)	24 (1.4)

Wedzicha JA. N Engl J Med 2016;374:2222.

in group D COPD patietns



BDP/FOR/GLY *vs* IND/GLY : Mortality

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BDP/FOR/GLY 87/5/9µg bid *vs* IND/GLY 85/43 µg for **52 weeks**.
Primary endpoint: **moderate-to-severe AE rate**

Prespecified analysis

	BDP/FF/G (n=764)	IND/GLY (n=768)	
Death	3 (<1%)	8 (1%)	*P*=0.13
Adverse events leading to death	16 (2%)	21 (3%)	*P*=0.41

Papi A. Lancet 2018;391:1076.

FF/VI/UMEC *vs* VIL/UMEC : mortality

Double-blind RCT (IMPACT). COPD pts FEV1<50%+AE≥1/yr or 50-80%+AE≥2 /yr (**CAT 20.1±6.1**)
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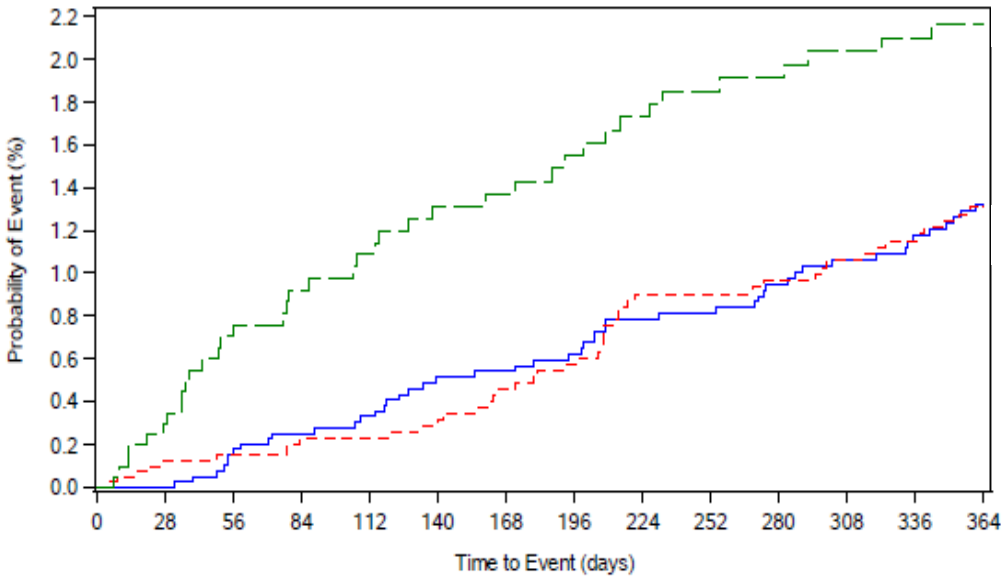
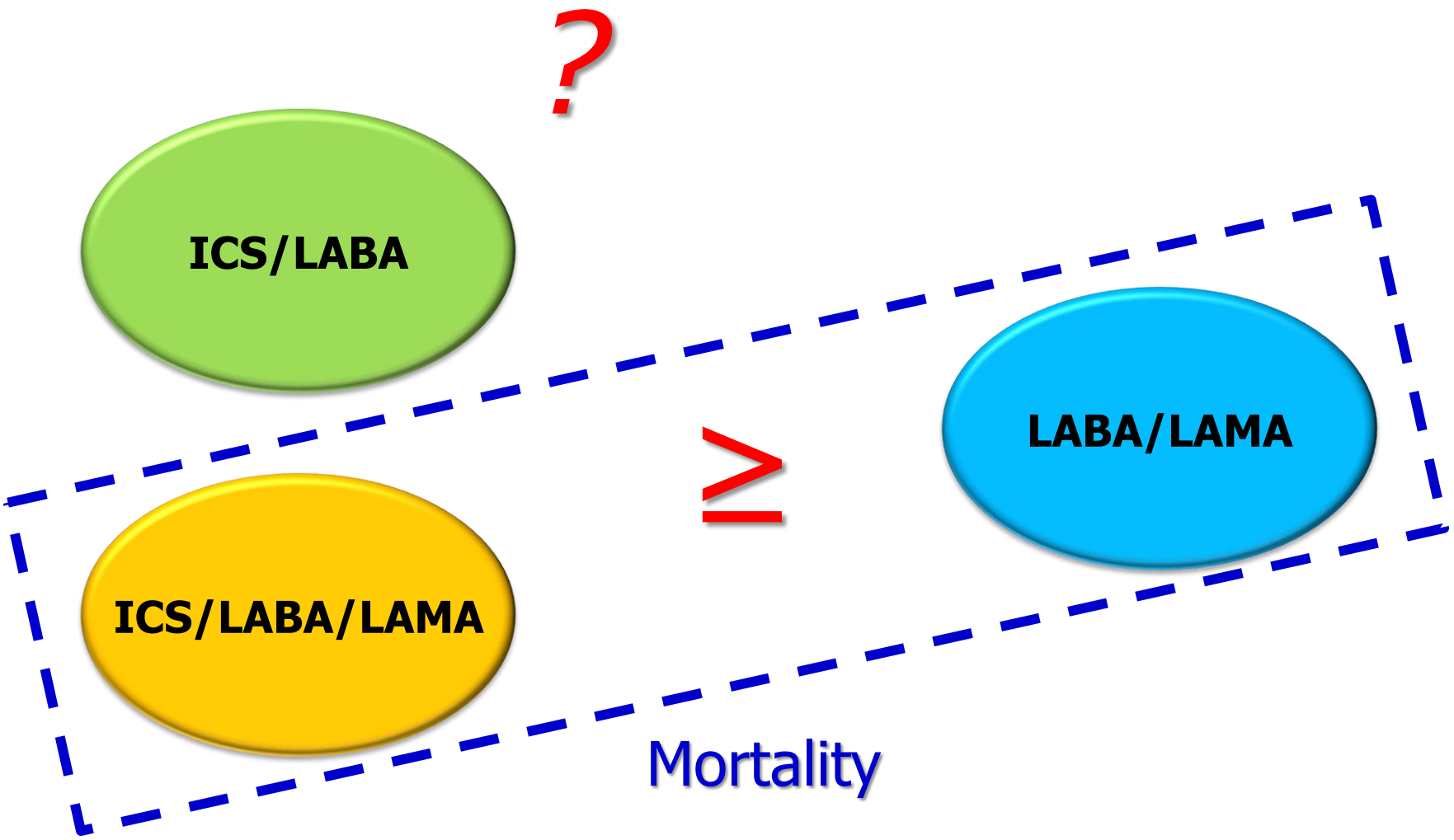


UMEC/VI 62.5/25
FF/VI 100/25
FF/UMEC/VI 100/62.5/25

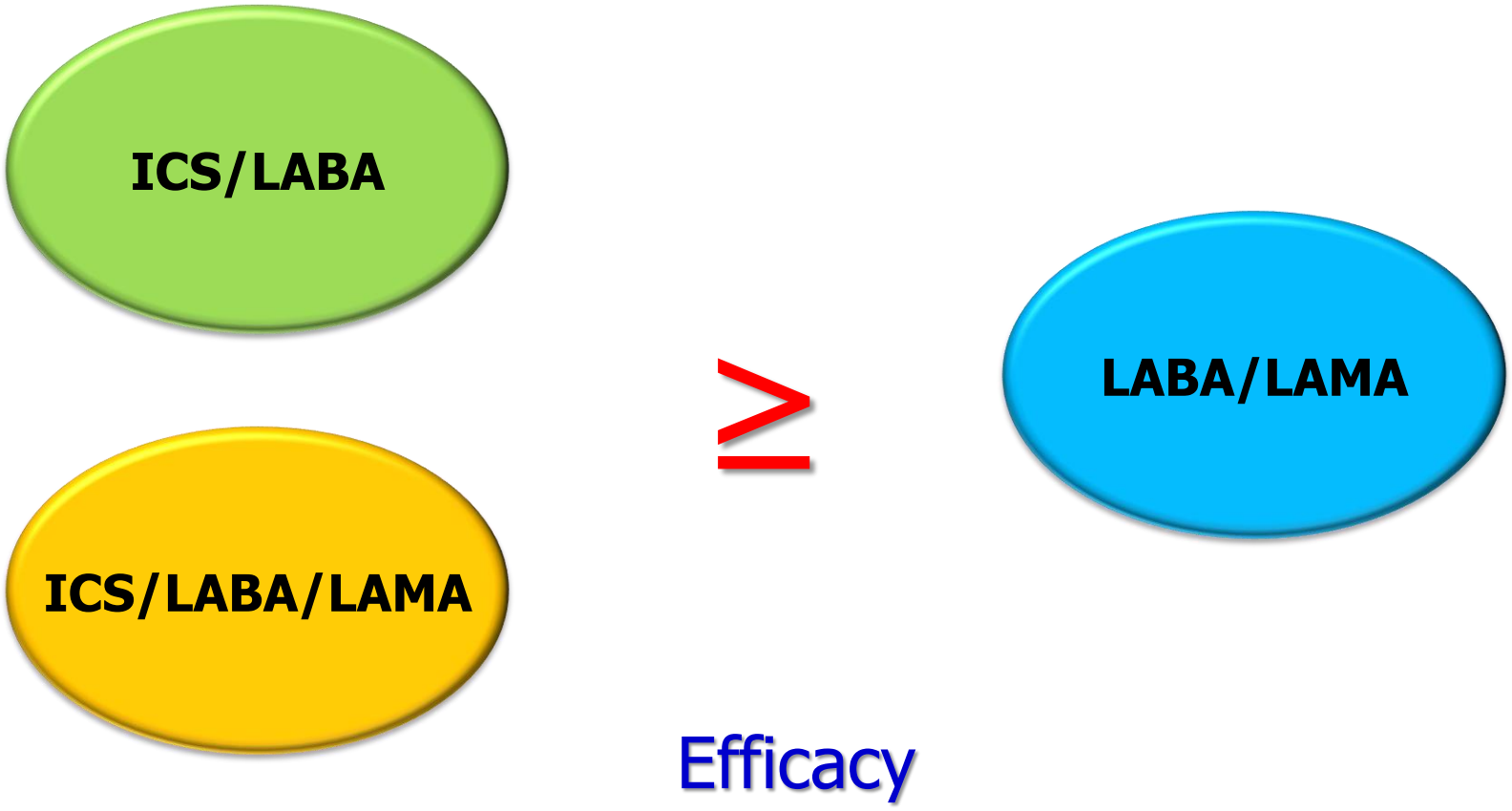
1 *P*=0.02
2 *P*=0.78
3 *P*=0.01

Lipson DA. N Engl J Med 2018 (Epub).

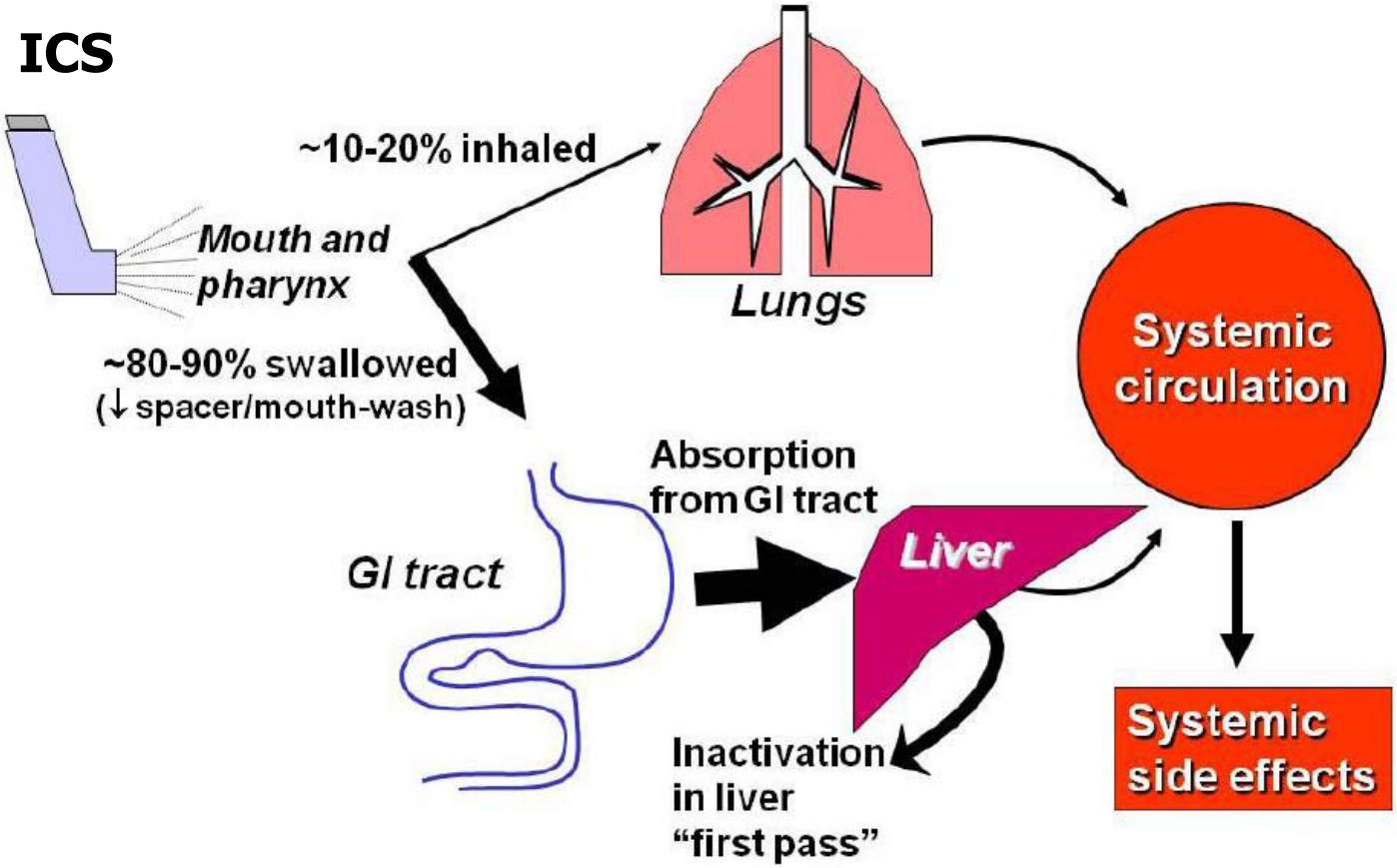
in group D COPD patietns



in group D COPD patietns



ICS : A/E



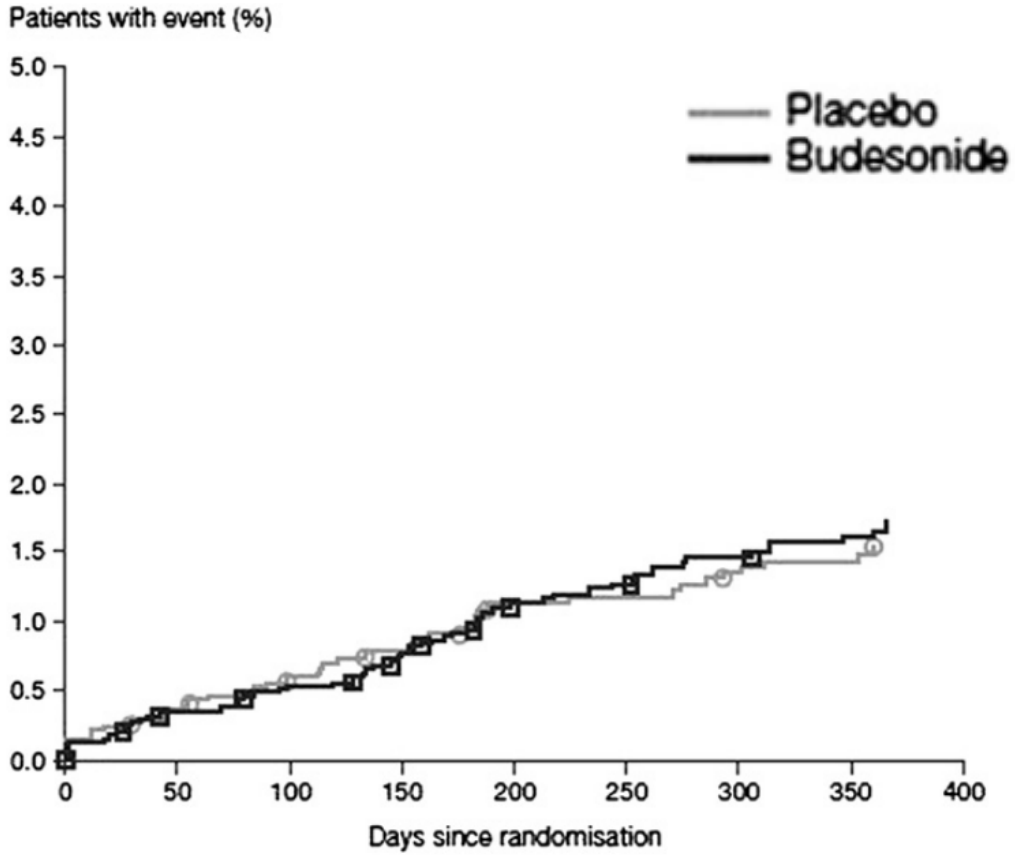
Lung A/E
TB
Pneumonia

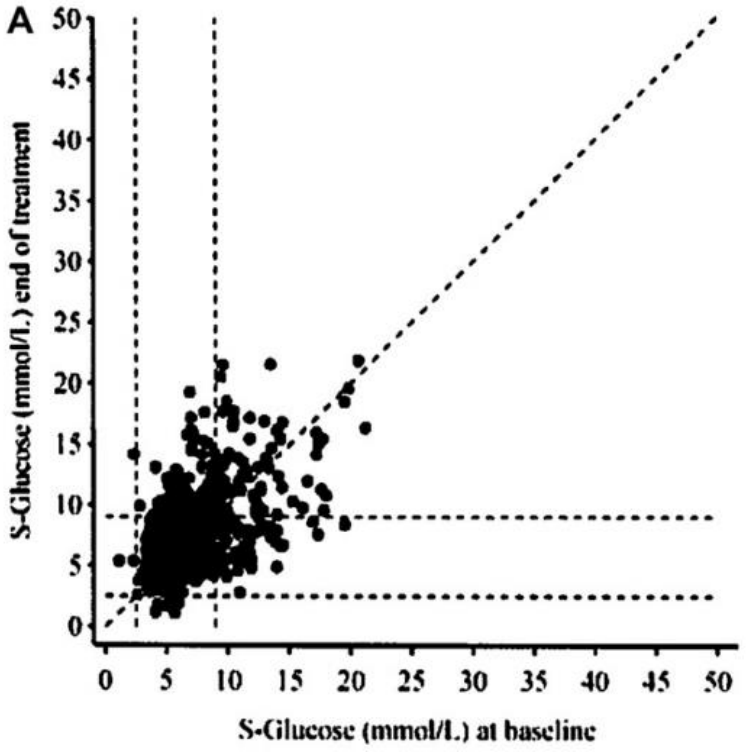
Systemic A/E
Diabetes
Osteoporosis
Fracture
Cataract
Myopathy
Weight gain
Infection

Barnes PJ. Pharmaceuticals 2010;3:514.

ICS use ⇨ DM⇧ (x)

Analysis for RCTs. Asthma pts (26 trials, n=14,983) and **COPD pts** (**8 trials, n=8,259**)

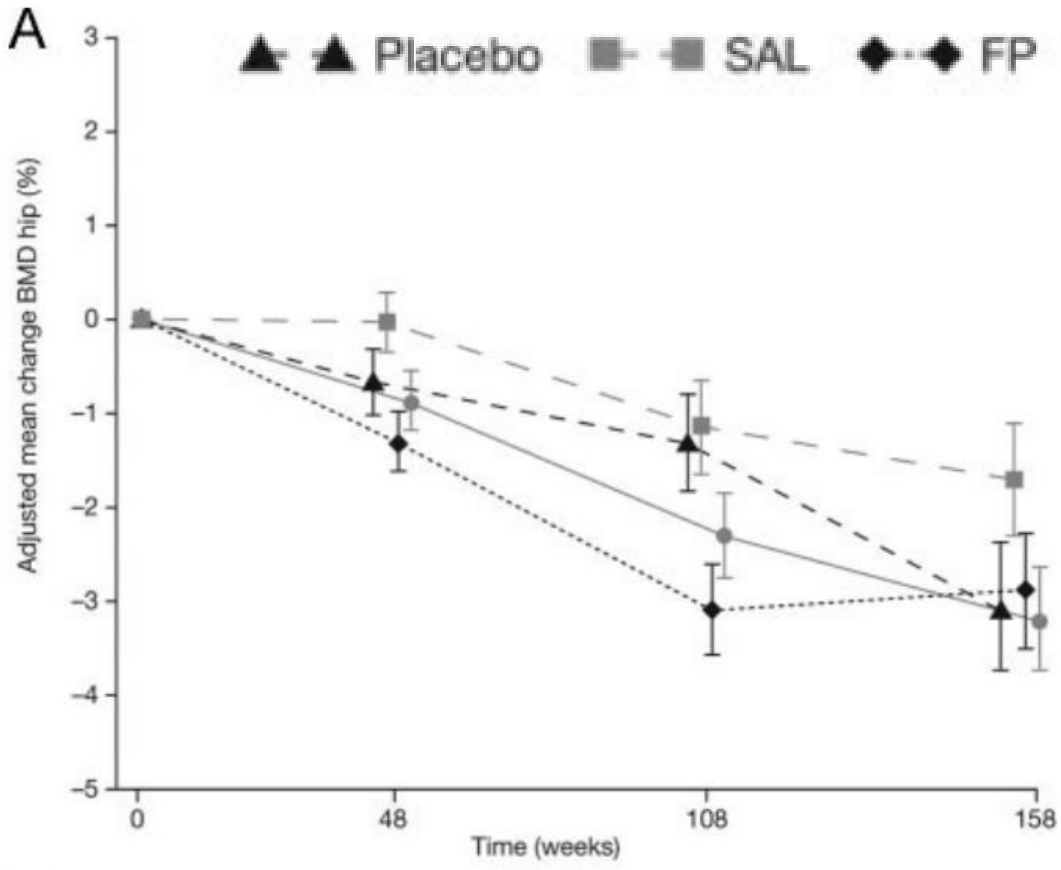




O'Byrne PM. Respir Med 2012;106:1487.

ICS use ⇨ BMD⇩ (x)

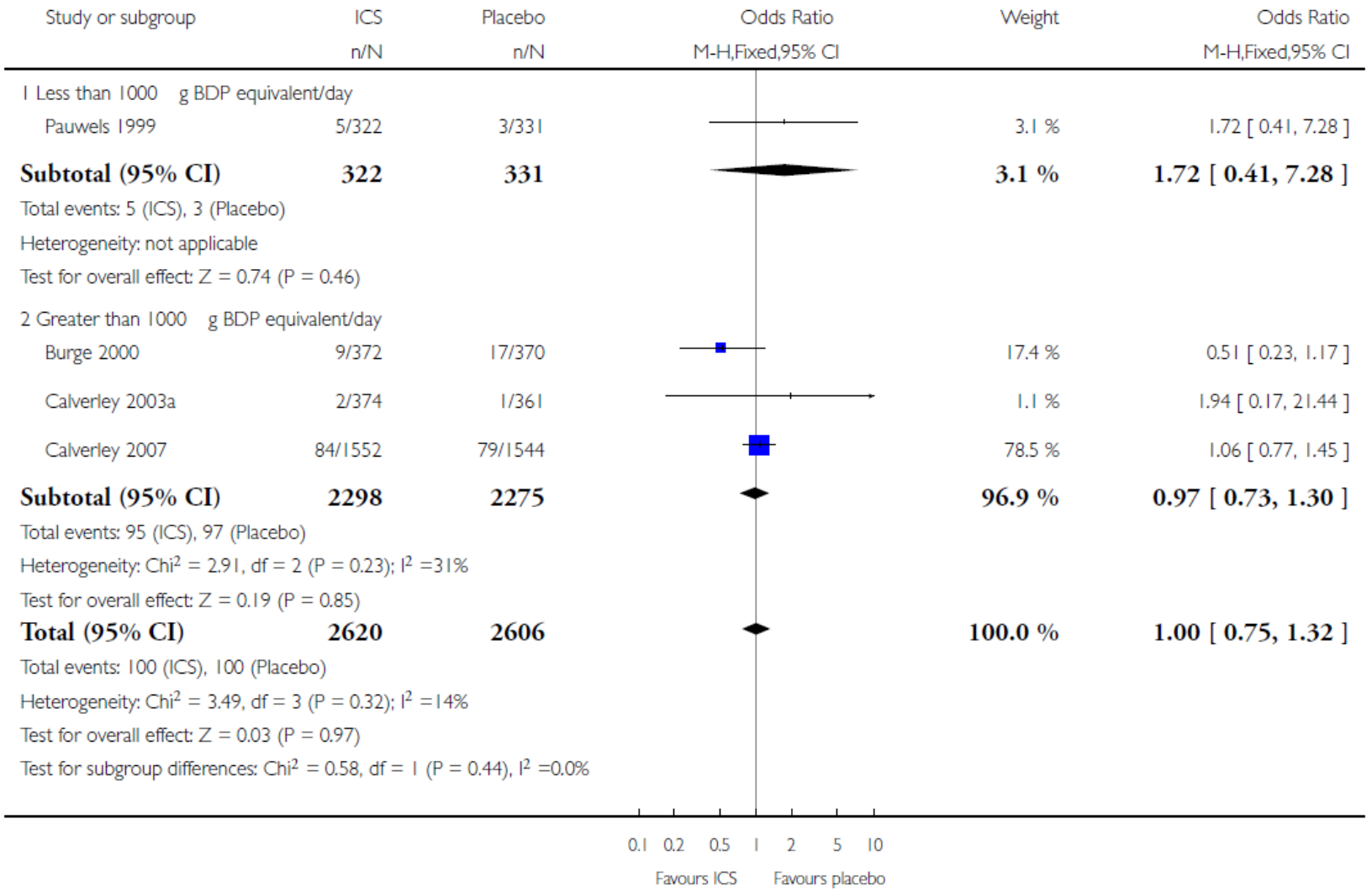
Double-blind, multicenter RCT (TORCH). COPD patients with FEV1<60% (**N=6,184**).
FP (ICS) *vs* **SAL (LABA)** *vs* **FP + SAL (ICS/LABA)** *vs* **PLA** for **3 years**.
Primary endpoint: **overall mortality**



Ferguson GT. Chest 2009;136:1456.

ICS use ⇨ Fracture⇧ (x)

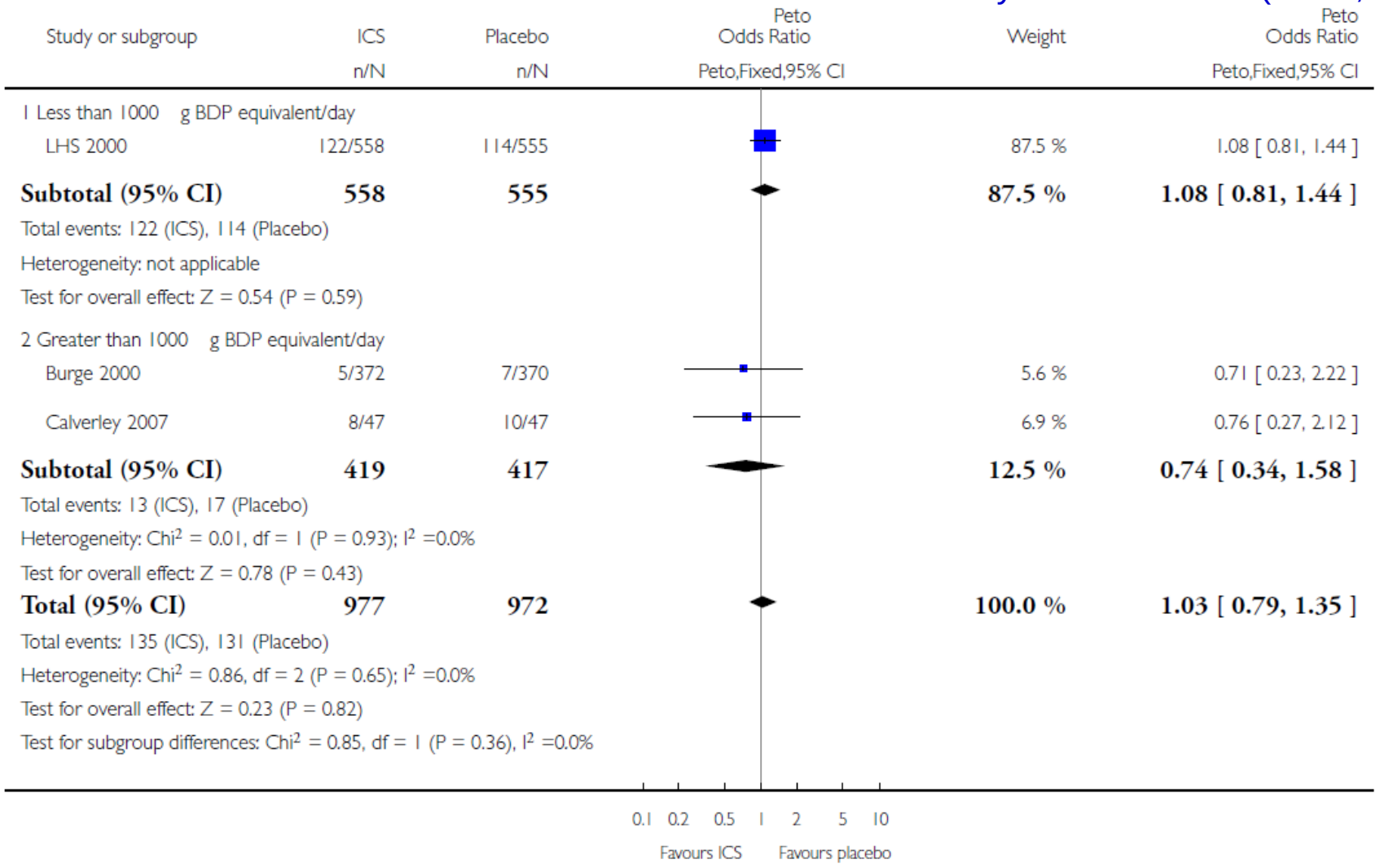
Meta-analysis for 55 RCTs (N=16,154)



Yang IA. Cochrane Database Syst Rev 2012;(7):CD002991.

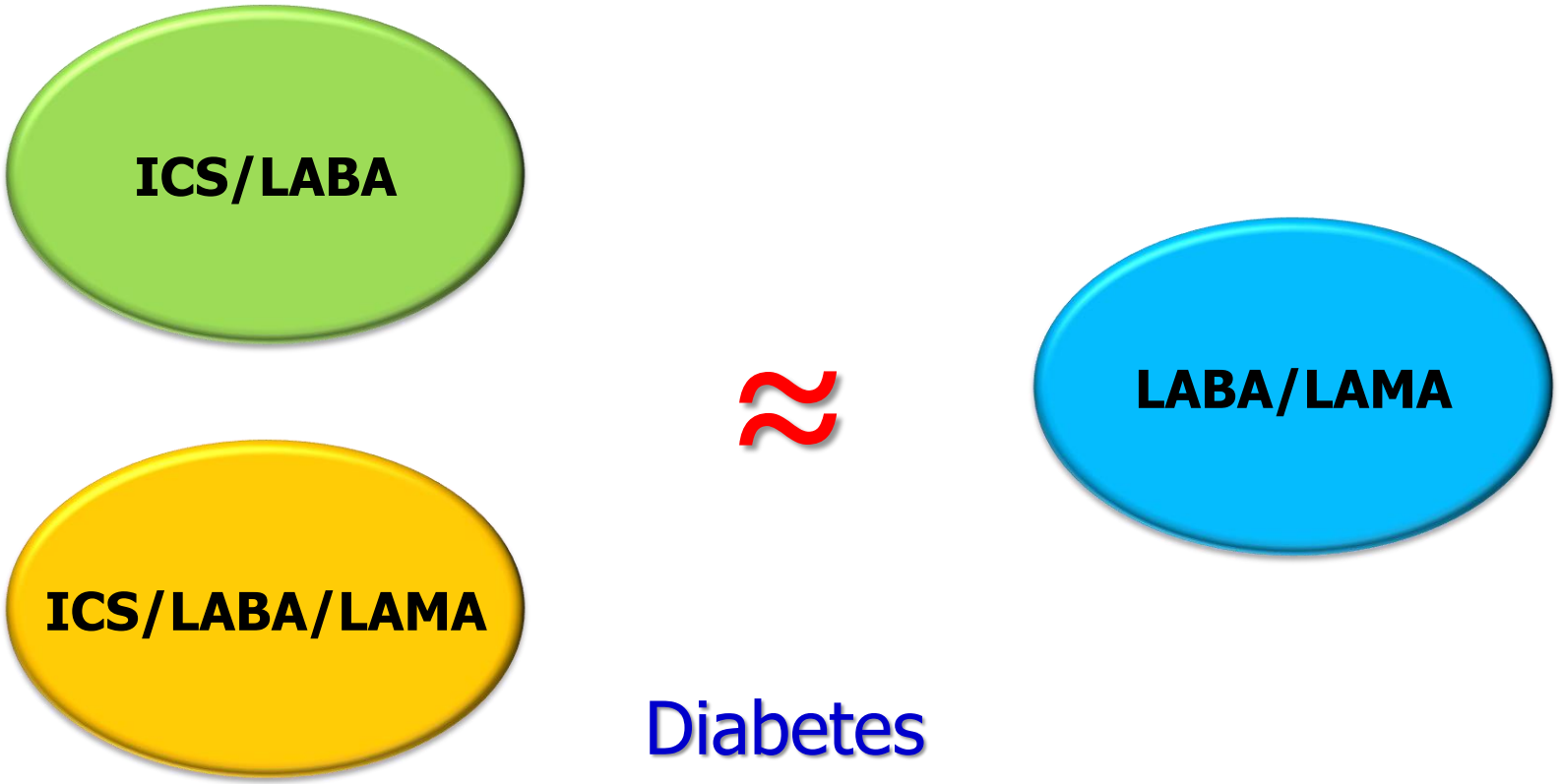
ICS use ⇨ Cataract⇧ (x)

Meta-analysis for 55 RCTs (N=16,154)



Yang IA. Cochrane Database Syst Rev 2012;(7):CD002991.

in group D COPD patietns

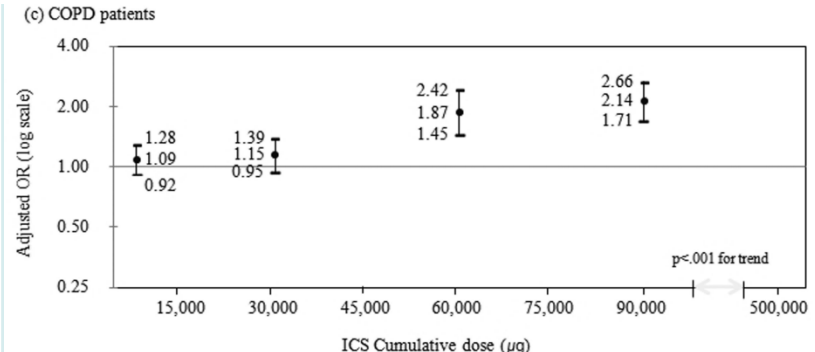


ICS use ⇨ TB ⇧

Retrospective case-control study using HIRA database. (**N=1,341,229**) TB cases (**n=4,139**).

Table 2 Risk of tuberculosis according to inhaler medication use

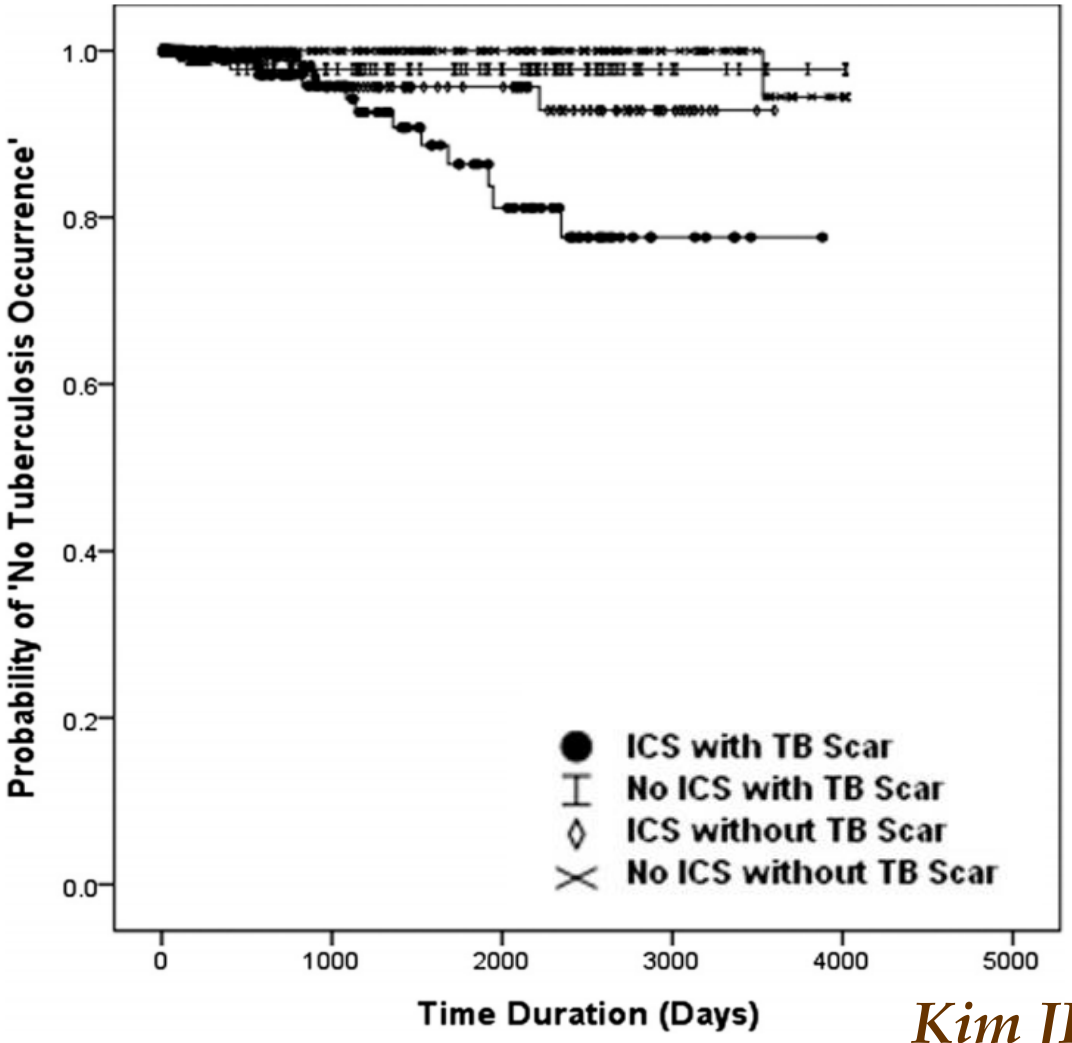
Type of use	Tuberculosis (N=4139), n (%)	Control (N=20 583), n (%)	Unadjusted OR (95% CI)	Unadjusted p Value	Adjusted* OR (95% CI)	Adjusted* p Value
Use of inhalers until index date						
ICS use						
Non-ICS users†	3294 (79.6)	17 007 (82.6)	1 (ref)		1 (ref)	
ICS users‡	845 (20.4)	3576 (17.4)	1.37 (1.23 to 1.52)	<0.001	1.20 (1.08 to 1.34)	0.001
OCS use						
Non-OCS users§	3773 (91.2)	19 606 (95.3)	1 (ref)		1 (ref)	
OCS users¶	366 (8.8)	977 (4.7)	2.13 (1.86 to 2.44)	<0.001	1.83 (1.58 to 2.12)	<0.001
ICS cumulative dose (μg)						
Median (Q1, Q3)	25 250 (7500 to 60 000)	15 000 (3000 to 30 000)				
p Value for trend**				<0.001		<0.001
0 dose	2969 (71.7)	14 345 (69.7)	1 (ref)		1 (ref)	
1–15 000	499 (12.1)	4129 (20.1)	0.55 (0.50 to 0.62)	<0.001	0.54 (0.49 to 0.61)	<0.001
15 001–45 000	303 (7.3)	1299 (6.3)	1.17 (1.01 to 1.36)	0.035	1.03 (0.89 to 1.21)	0.677
45 001–75 000	144 (3.5)	378 (1.8)	2.04 (1.66 to 2.51)	<0.001	1.72 (1.38 to 2.14)	<0.001
75 001+	224 (5.4)	432 (2.1)	2.92 (2.44 to 3.50)	<0.001	2.16 (1.77 to 2.63)	<0.001



Lee CH. Thorax 2013;68:1105.

ICS use ⇨ TB ⇧

Retrospective cohort study. COPD pts. (**N=616**) TB cases (**n=20**).

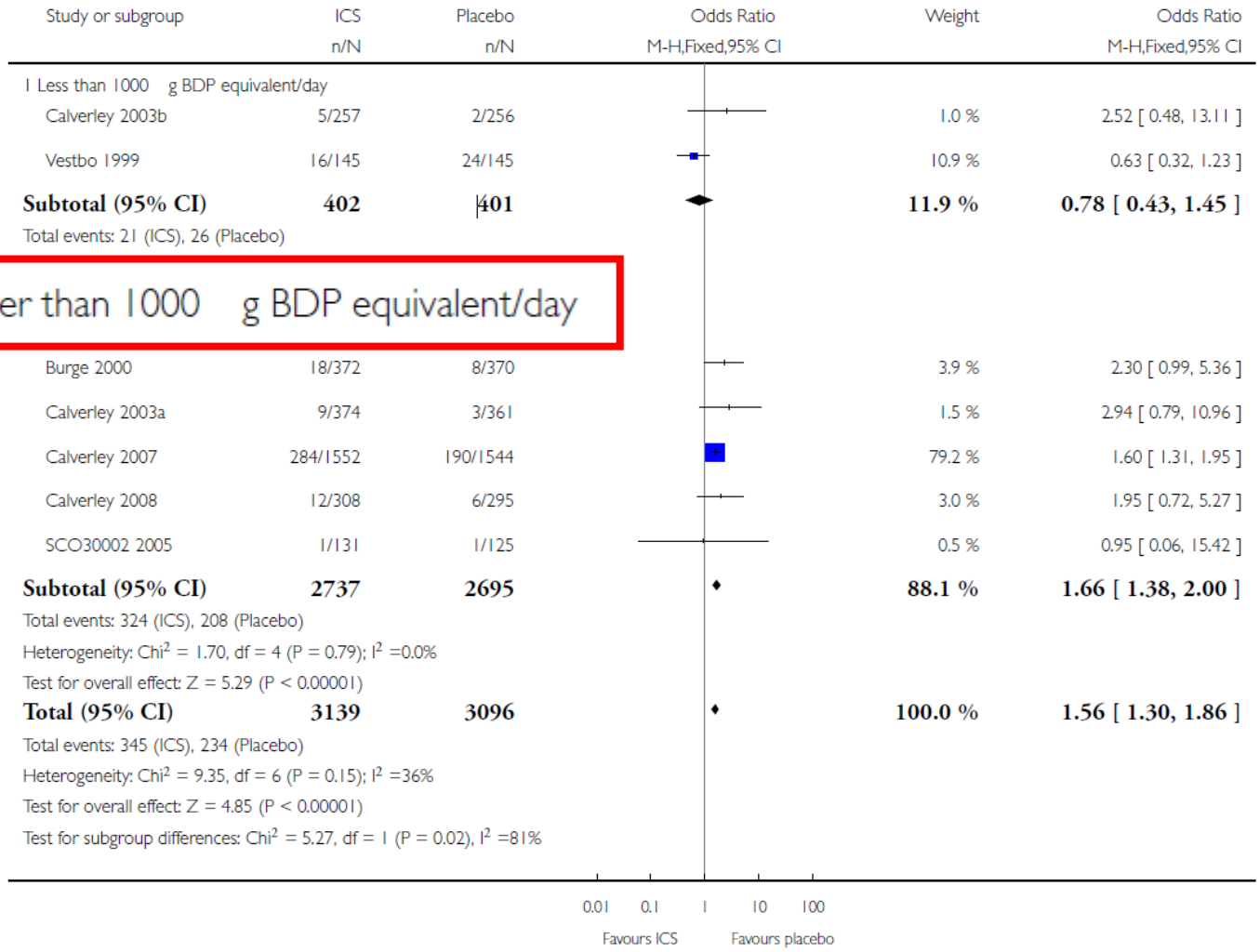


< 3% during upto 10 years

Kim JH. Chest 2013;143:1018.

ICS use ⇨ Pneumonia⇧

Meta-analysis for 55 RCTs (N=16,154)



Yang IA. Cochrane Database Syst Rev 2012;(7):CD002991.

FF/VI±UMEC *vs* VIL/UMEC : pneumonia

Double-blind RCT (IMPACT). COPD pts FEV1<50%+**AE≥1/yr** or 50-80%+**AE≥2 /yr** (**CAT 20.1±6.1**)
FF/VI/UMEC 100/25/62.5μg *vs* FF/VI *vs* UMEC/VIL for **52 weeks**. (**N=4,151+4,134+2,070**).
Primary endpoint: moderate-to-severe AE rate

Table 3. Adverse Events of Special Interest in the Intention-to-Treat Population.*

Event	Triple Therapy (N=4151)		Fluticasone Furoate–Vilanterol (N=4134)		Umeclidinium–Vilanterol (N=2070)	
	No. of Patients (%)	Rate per 1000 Patient-Yr (No. of Events)	No. of Patients (%)	Rate per 1000 Patient-Yr (No. of Events)	No. of Patients (%)	Rate per 1000 Patient-Yr (No. of Events)
Pneumonia	317 (8)	95.8 (356)	292 (7)	96.6 (334)	97 (5)	61.2 (104)

NNH, 37.5

Lipson DA. N Engl J Med 2018 (Epub).

BDP/FF/GLY *vs* IND/GLY : pneumonia

Double-blind RCT (TRIBUTE). COPD pts with FEV1<50%+**AE≥1 /yr**. (**N=1,532**)
BDP/FOR/GLY 87/5/9µg bid *vs* IND/GLY 85/43 µg for **52 weeks**.
Primary endpoint: **moderate-to-severe AE rate**

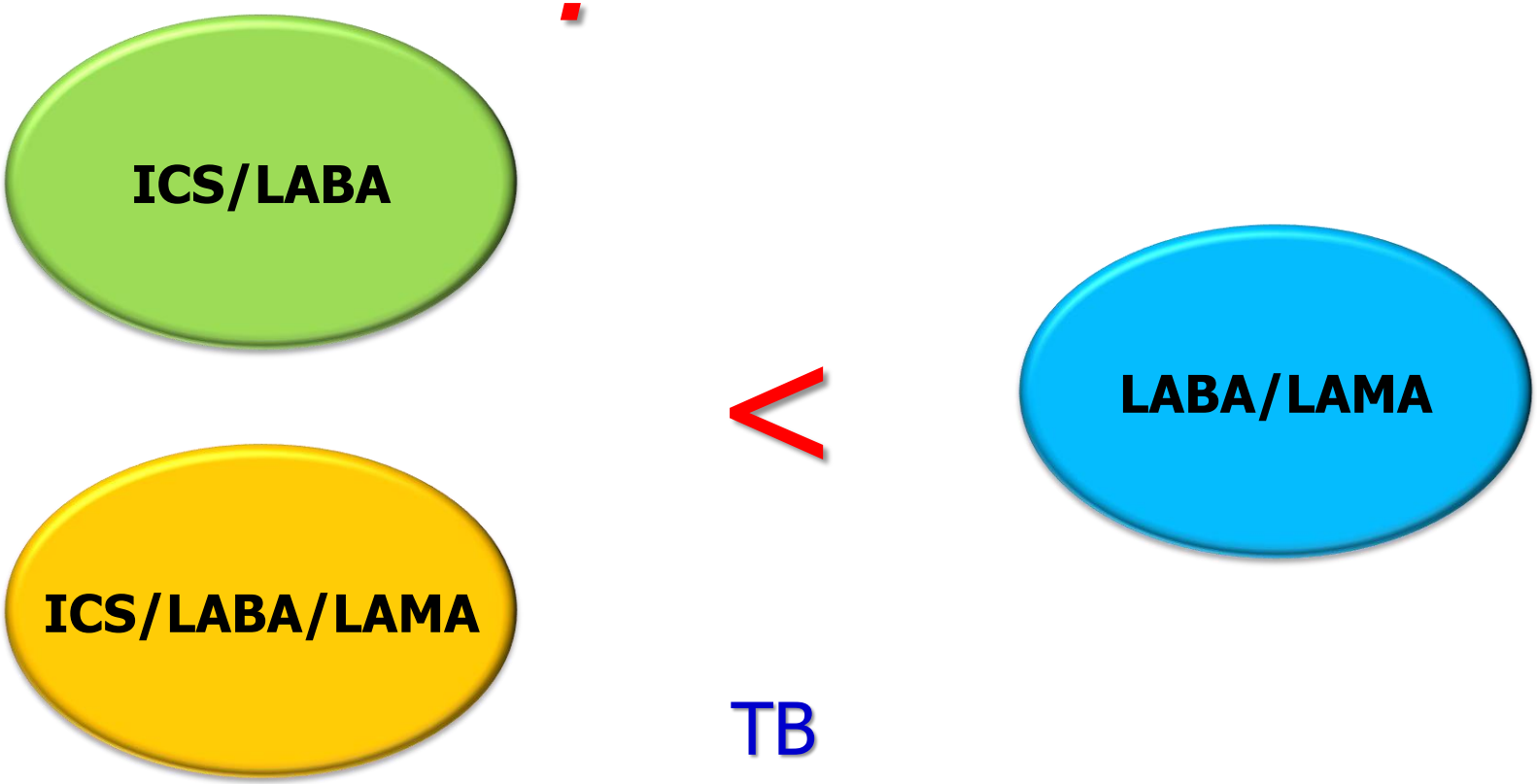
	BDP/FF/G (n=764)	IND/GLY (n=768)
Pneumonia	18 (2%)	17 (2%)

NNH, 701.9

Papi A. Lancet 2018;391:1076.

in group D COPD patietns

?

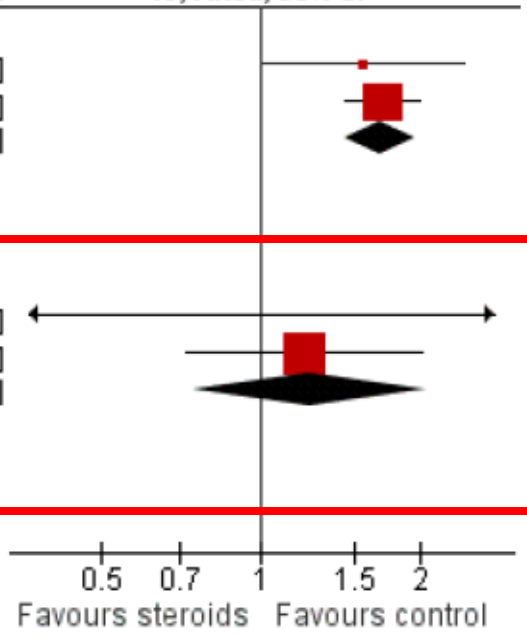


TB
Pneumonia

ICS ⇨ pneumonia⇧ : really important?

Meta-analysis for **43 RCTs**. (**N=31,397**)

Study or Subgroup	log[Odds Ratio]	SE	Steroids Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
4.1.1 Non-fatal serious adverse pneumonia events						
Budesonide	0.4824	0.2461	3948	2524	11.5%	1.62 [1.00, 2.62]
Fluticasone	0.5766	0.0887	10983	8521	88.5%	1.78 [1.50, 2.12]
Subtotal (95% CI)			**14931**	**11045**	**100.0%**	**1.76 [1.50, 2.07]**
Heterogeneity: Chi² = 0.13, df = 1 (P = 0.72); I² = 0%						
Test for overall effect: Z = 6.78 (P < 0.00001)						
4.1.3 Mortality due to pneumonia						
Budesonide	1.4951	2.1247	962	549	1.8%	4.46 [0.07, 286.99]
Fluticasone	0.207	0.2847	10997	8535	98.2%	1.23 [0.70, 2.15]
Subtotal (95% CI)			**11959**	**9084**	**100.0%**	**1.26 [0.72, 2.19]**
Heterogeneity: Chi² = 0.36, df = 1 (P = 0.55); I² = 0%						
Test for overall effect: Z = 0.81 (P = 0.42)						



Kew K. Cochrane Database Syst Rev 2014;CD010115.

True pneumonia ?

2 double-blind RCTs. COPD pts with FEV1 ≤70%, ≥10PY, AE ≥1/yr. (**N=1,622 + 1,633**).
Fluticasone furoate(FF)/Vilanterol(VI) 200/25 *vs* **FF/VI 100/25** *vs* **FF/VI 50/25** *vs* **VI 25µg**.
Primary end point: **the yearly rate of moderate-severe AE**.

	25 µg vilanterol (n=818)	50 µg fluticasone furoate+ 25 µg vilanterol (n=820)	100 µg fluticasone furoate+ 25 µg vilanterol (n=806)	200 µg fluticasone furoate+ 25 µg vilanterol (n=811)
Pneumonia				
Total events	28	54	58	65
Radiograph taken (% of total events)	26 (93%)	44 (81%)	50 (86%)	56 (86%)
Events for which radiograph showed infiltrates	15	27	31	40
Patients with serious pneumonia* (%)	8 (1%)	24 (3%)	25 (3%)	23 (3%)

"Actually miscellaneous lower respiratory infectious syndromes, such as mild COPD exacerbation?"

Dransfield MT. Lancet Respir Med 2013;1:210.
Finney L. Lancet Respir Med 2014;2:919.

Prior ICS use ⇨ Parapneumonic effusion⇩

A prospective study in Spain. Pts with CAP admitted to ER. (**N=3,612**; ICS user: 633 (17%))
Outcome: **Parapneumonic effusion (PPE)**

TABLE 4. ASSOCIATION BETWEEN ICS AND PPE BEFORE AND AFTER PROPENSITY SCORE MATCHING*

Variable	OR	95% CI	*P*
PPE of any category			
Crude (full cohort)	0.38	0.26–0.55	<0.001
Propensity score matching	0.40	0.23–0.69	0.001
PPE confirmed by thoracocentesis (categories 2, 3, and 4 of ACCP)			
Crude (full cohort)	0.29	0.17–0.47	<0.001
Propensity score matching	0.26	0.12–0.57	0.001
Complicated PPE and empyema (categories 3 and 4 of ACCP)			
Crude (full cohort)	0.33	0.16–0.65	0.001
Propensity score matching	0.32	0.12–0.90	0.03
Empyema			
Crude (full cohort)	0.24	0.08–078	0.018
Propensity score matching	0.14	0.02–1.15	0.067

Sellares J. Am J Respir Crit Care Med 2013;187:1241.

Prior ICS use ⇨ Pneumonia mortality ⇩

Retrospective cohort study using databases. Pts with both a preexisting COPD and a discharge diagnosis of pneumonia. (**N=15,768**; ICS user: 8,271, non-ICS user: 7,497) Outcome: **mortality**

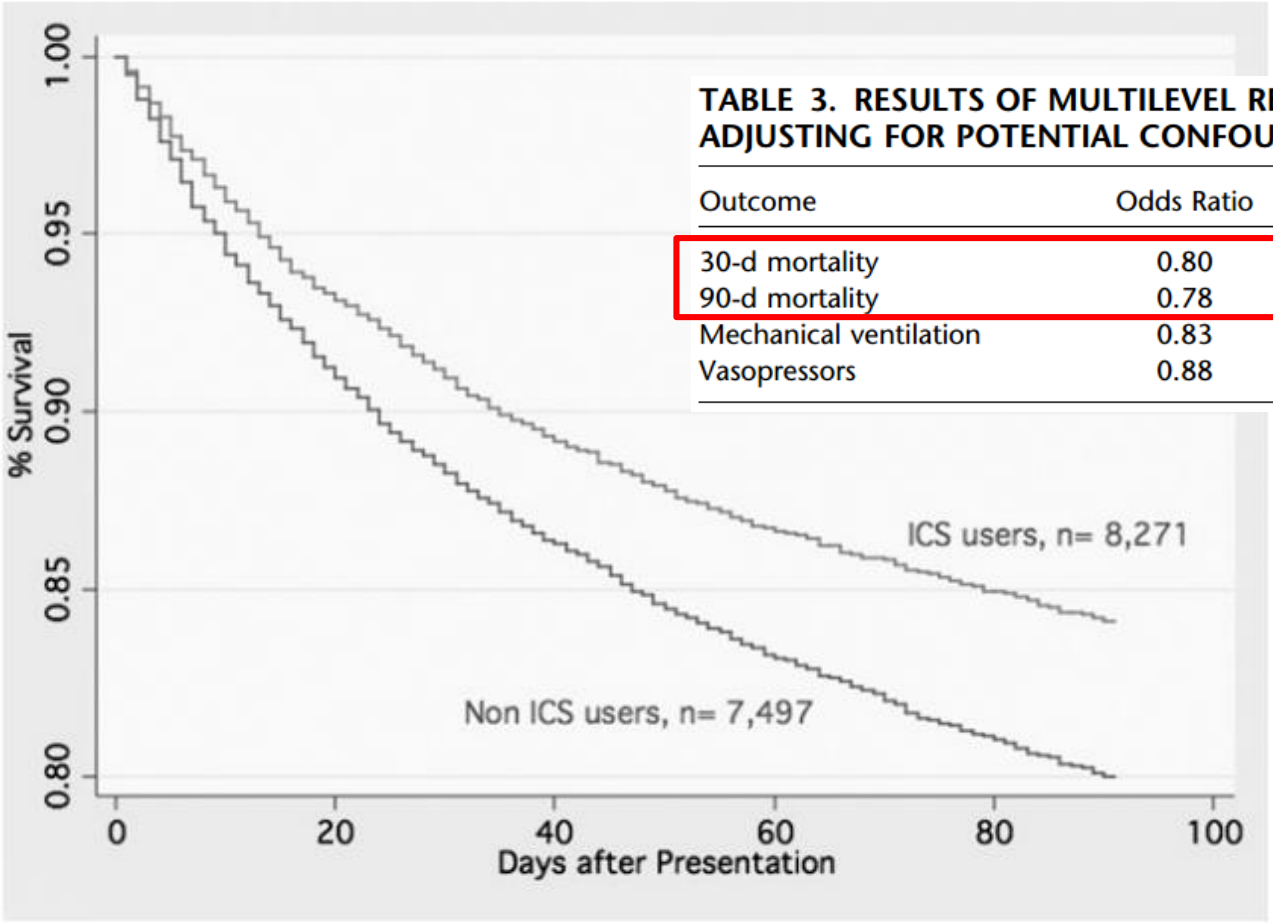
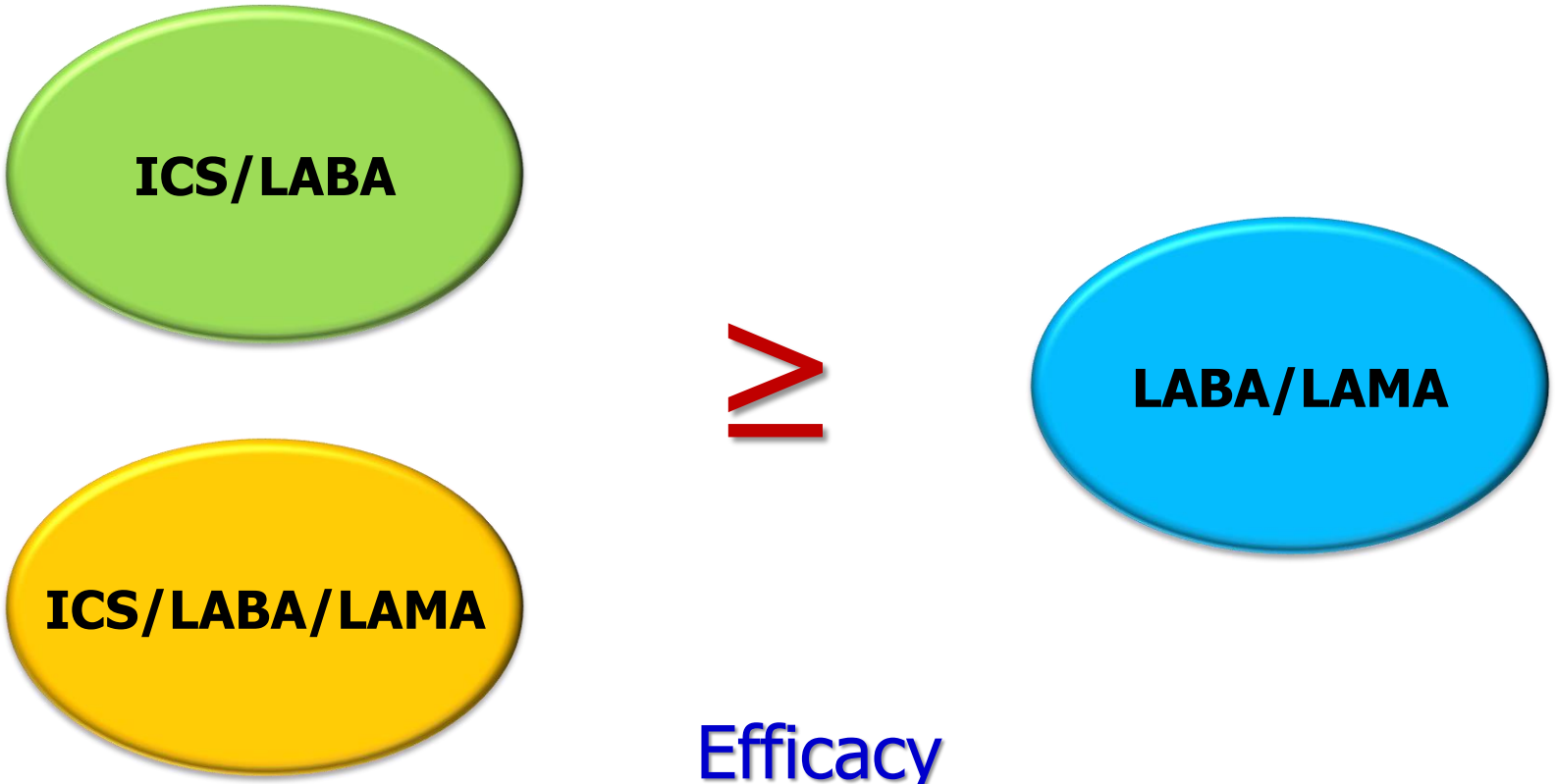


TABLE 3. RESULTS OF MULTILEVEL REGRESSION MODELS AFTER ADJUSTING FOR POTENTIAL CONFOUNDERS*

Outcome	Odds Ratio	95% Confidence Interval
30-d mortality	0.80	0.72–0.89
90-d mortality	0.78	0.72–0.85
Mechanical ventilation	0.83	0.72–0.94
Vasopressors	0.88	0.74–1.04

Chen D. Am J Respir Crit Care Med 2011;184:312.

in group D COPD patietns



Efficacy

Safety (except TB risk)