2016-11-17

COPD 최신 치료 지견

정지예
연세대학교 의과대학 내과학교실
세브란스병원 호흡기내과

Obama Announces $215 Million Precision-Medicine Genetic Plan

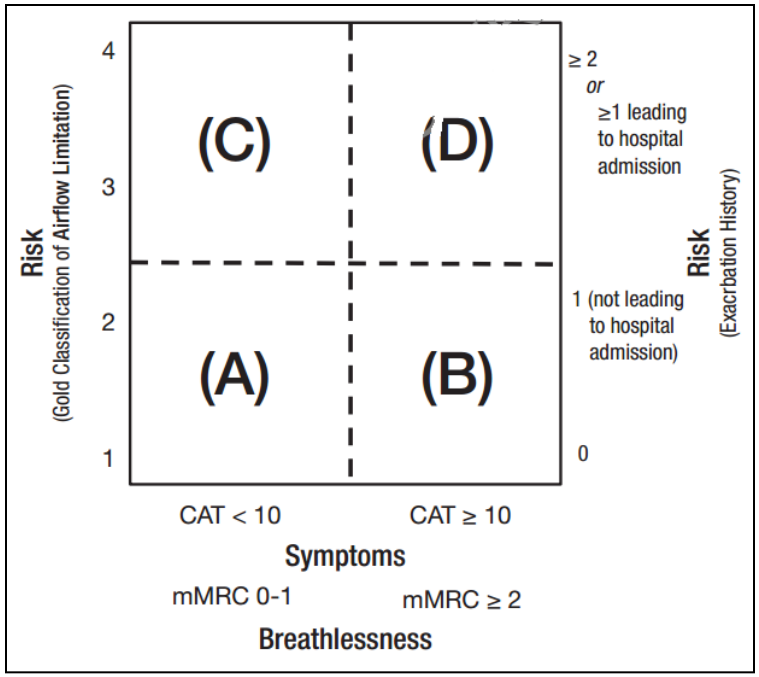
30 Jan. 2015

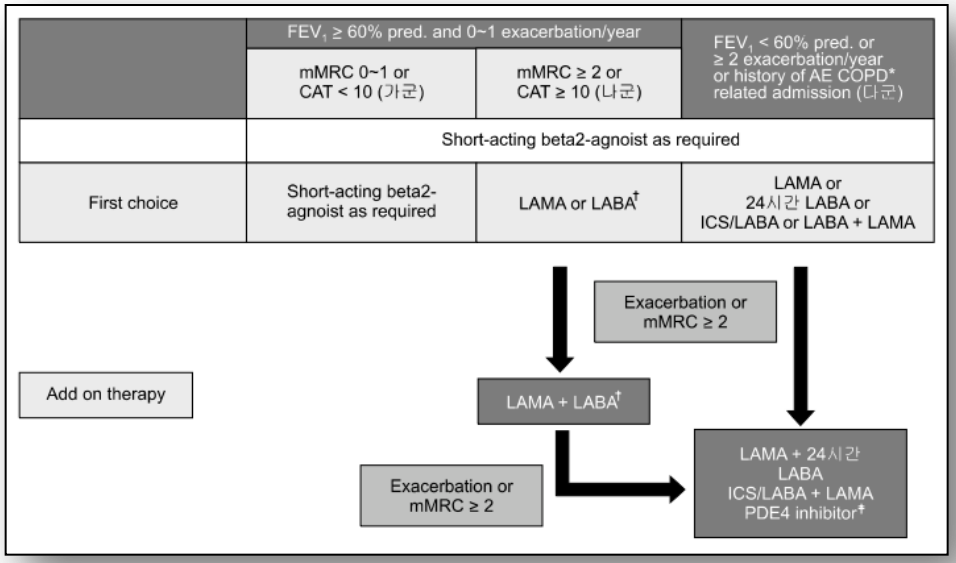
https://www.whitehouse.gov/precision-medicine

COPD

Phenotype (clinical)

Endotype (biological)

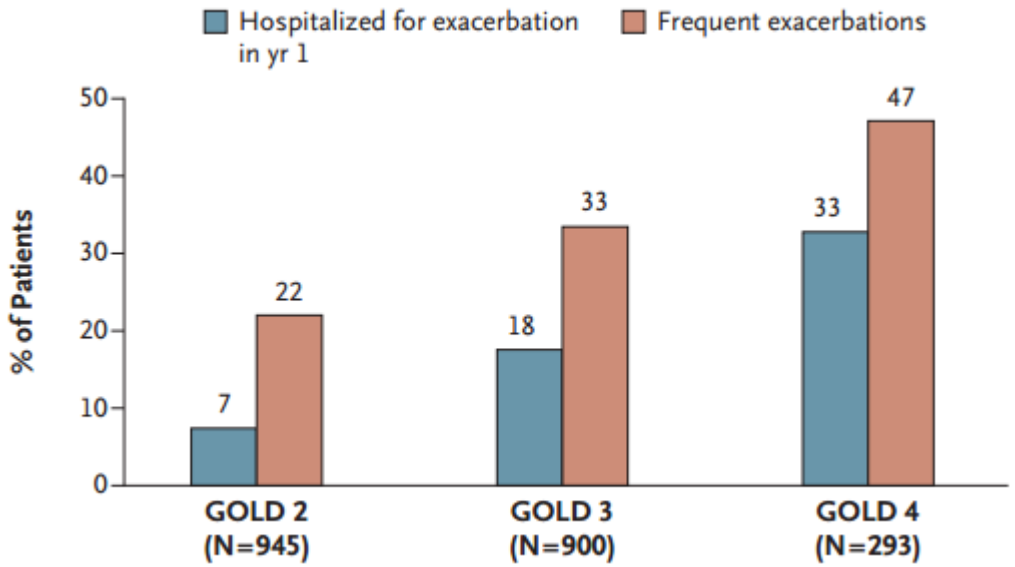




Is FEV_1 useful for guiding treatment decisions?

ECLIPSE

Factors	≥ 2 vs. 0		1 vs. 0		≥ 2 vs. 1	
	OR	P-value	OR	P-value	OR	P-value
AE previous yr vs. none	5.72	< 0.001	2.24	< 0.001	2.55	< 0.001
FEV_1, 100mL ↓	1.11	< 0.001	1.06	< 0.001	1.05	< 0.001
SGRQ, 4 points ↑	1.07	< 0.001	1.01	0.38	1.06	< 0.001
Reflux vs. no	2.07	< 0.001	1.61	< 0.001	1.29	< 0.001
WBC, 1000/mm3 ↑	1.08	0.002	1.02	0.45	1.06	0.007



Hurst et al. NEJM 2010

Is FEV_1 useful for guiding treatment decisions?

CODP Gene

C1 or D1: FEV1 <50% predicted
C2 or D2: frequent history of COPD exacerbation (≥2 events per past 12 months)
C3 or D3 both airfl ow limitation and history of frequent COPD exacerbation

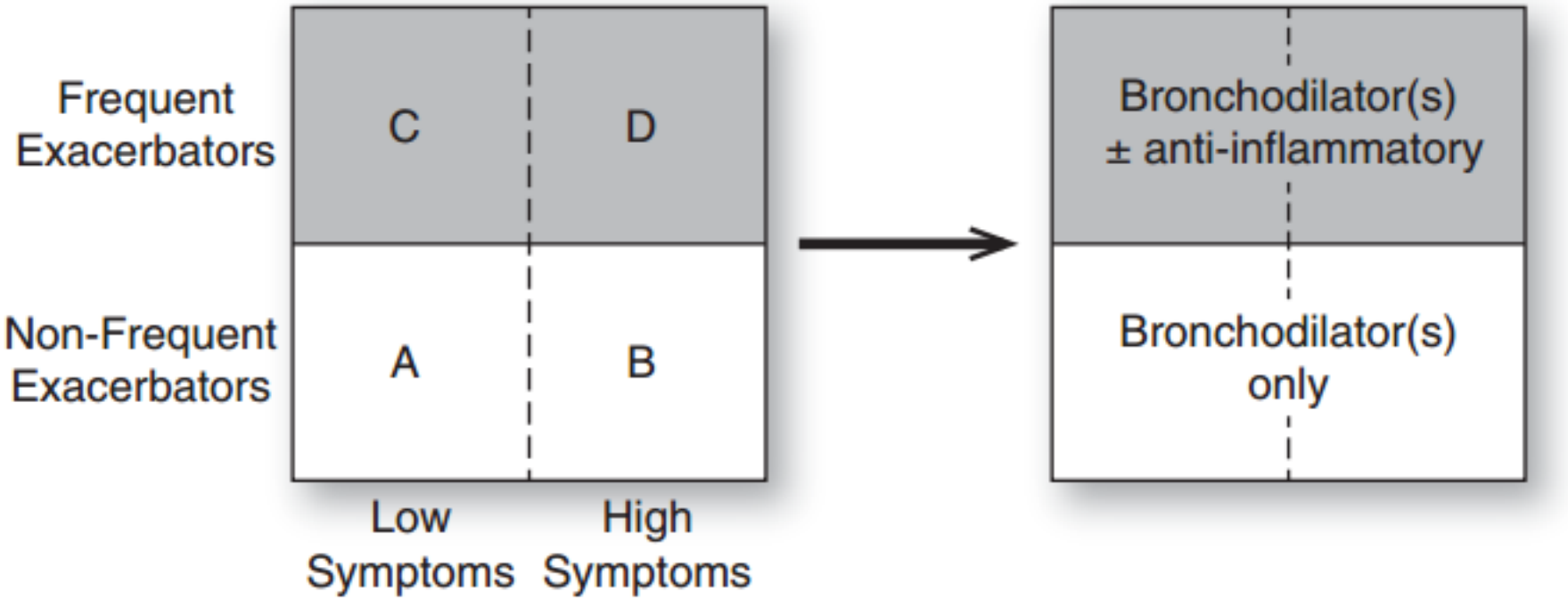
Events/year	A	B	C1	C2	C3	D1	D2	D3
N (%)	1317 (29)	1109 (25)	173 (4)	38 (1)	10 (<1)	1182 (26)	252 (6)	103 (9)
Total AE rate in previous yr	0.07	0.27	0.18	2.45	2.50	0.35	2.90	3.10
Total AE	0.17	0.55	0.58	0.52	1.39	0.89	1.34	1.86
Severe AE	0.02	0.13	0.06	0.13	0.11	0.27	0.57	0.62

UPLIFT

	Median time to 1st exacerbation		Mean number of exacerbation		Median time to 1st exacerbation, admission to hospital		Median number to 1st exacerbation, admission to hospital	
	months	*P*-value	per patient-year	*P*-value	months	*P*-value	per patient-year	*P*-value
GOLD II	0.82	< 0.001	0.80	< 0.0001	0.74	0.001	0.80	0.082
GOLD III	0.87	0.002	0.88	0.003	0.93	0.270	0.97	0.705
GOLD IV	0.99	0.956	0.92	0.397	0.85	0.225	0.99	0.963

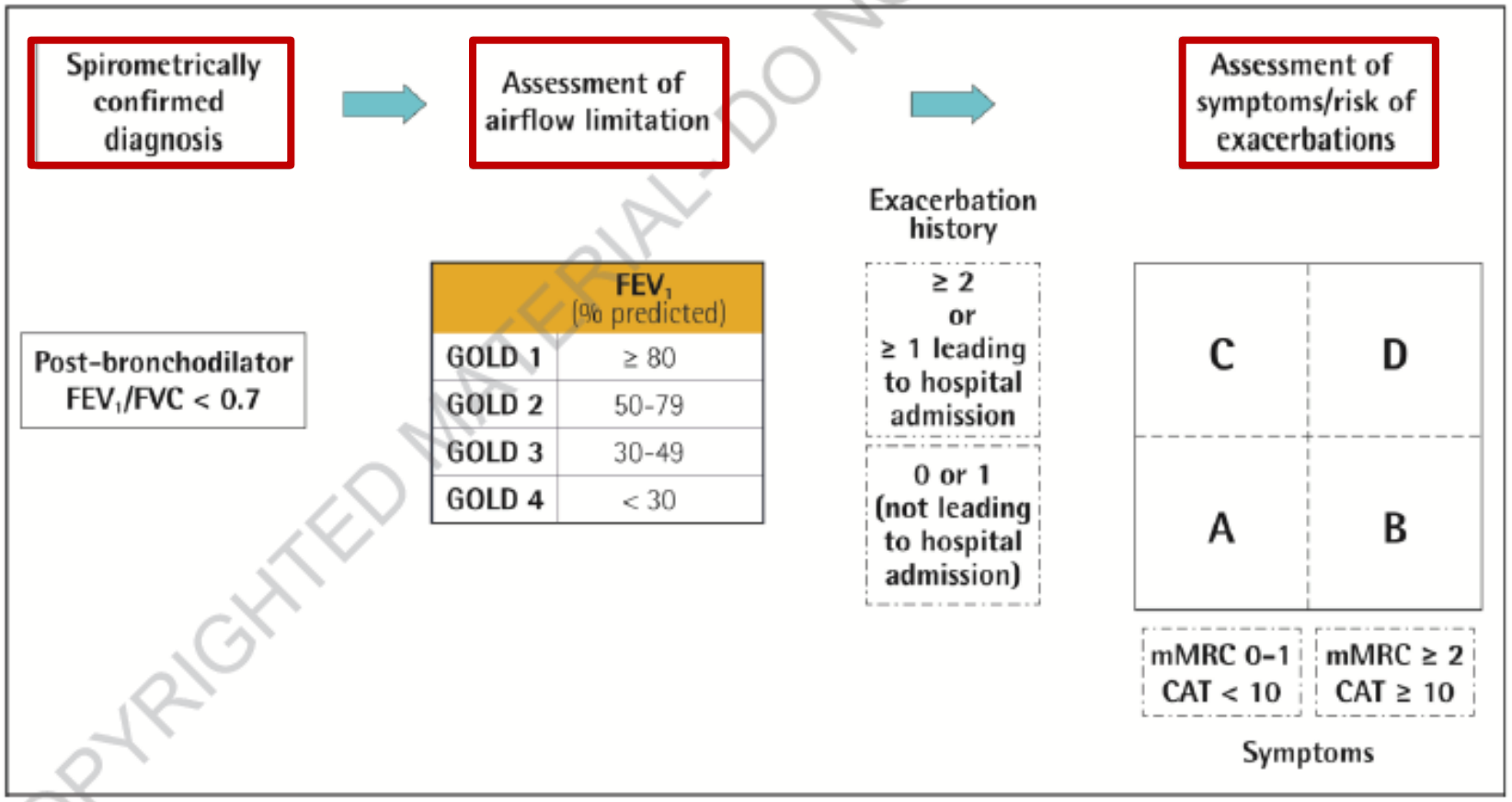
Han et al. Lancet Respir Med 2013
Decramer et al. Lancet 2009

FEV_1 Free Approach to COPD



Singh et al. Am Jr Respi Cri Care Med 2016

Redefined ABCD assessment



GOLD 2017

Initial Pharmacological Treatment

	$FEV_1 \geq 60\%$ pred. and 0~1 exacerbation/year		$FEV_1 < 60\%$ pred. or ≥ 2 exacerbation/year or history of AE COPD* related admission (다군)
	mMRC 0~1 or CAT < 10 (가군)	mMRC ≥ 2 or CAT ≥ 10 (나군)	
	Short-acting beta2-agnoist as required		
First choice	Short-acting beta2-agnoist as required	LAMA or LABA†	LAMA or 24시간 LABA or ICS/LABA or LABA + LAMA

Add on therapy

Exacerbation or mMRC ≥ 2

LAMA + LABA†

Exacerbation or mMRC ≥ 2

LAMA + 24시간 LABA
ICS/LABA + LAMA
PDE4 inhibitor‡

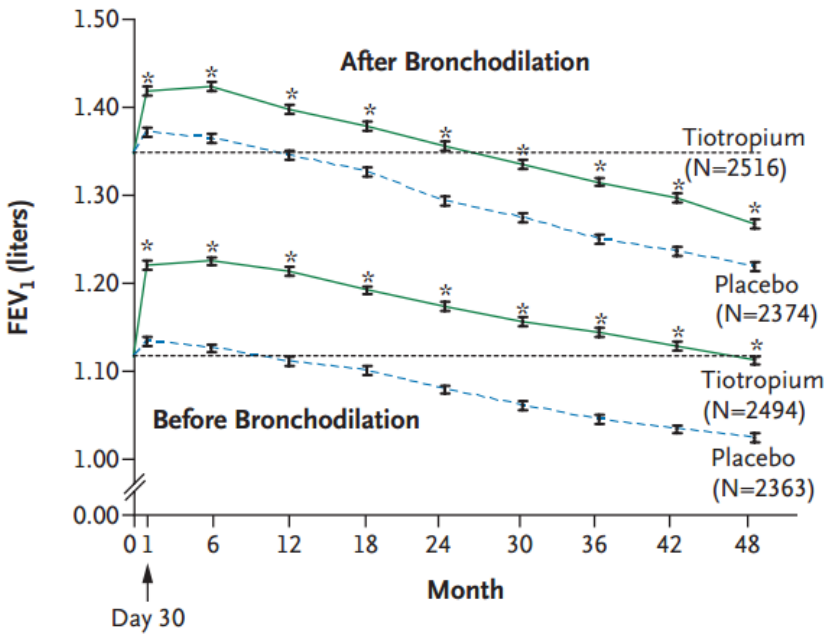
국내 진료 지침 2014

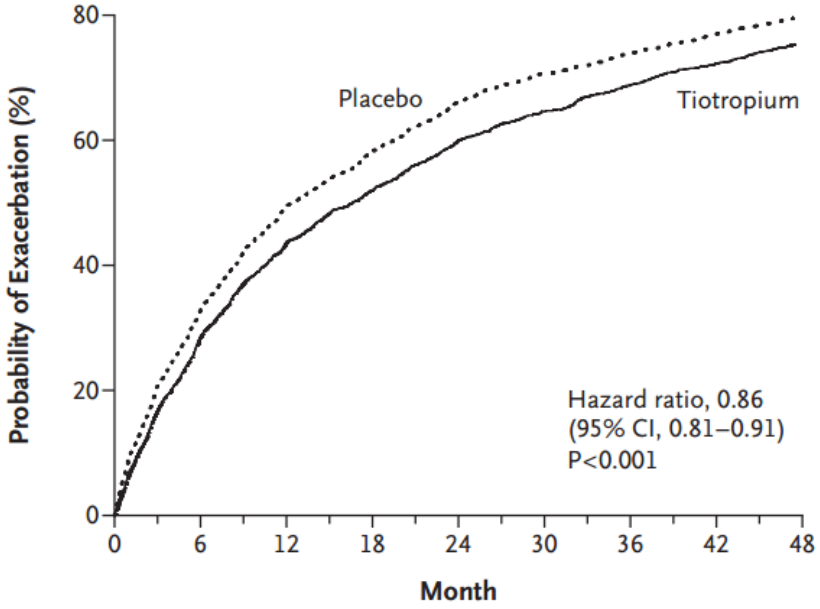
UPLIFT

LAMA vs Placebo

Inclusion: FEV_1 ≤ 70% pred. (GOLD II (46%), III (44%), IV (8%))
- Tiotropium (n=1887)
- Placebo (n=1648)

Duration: 4 yrs



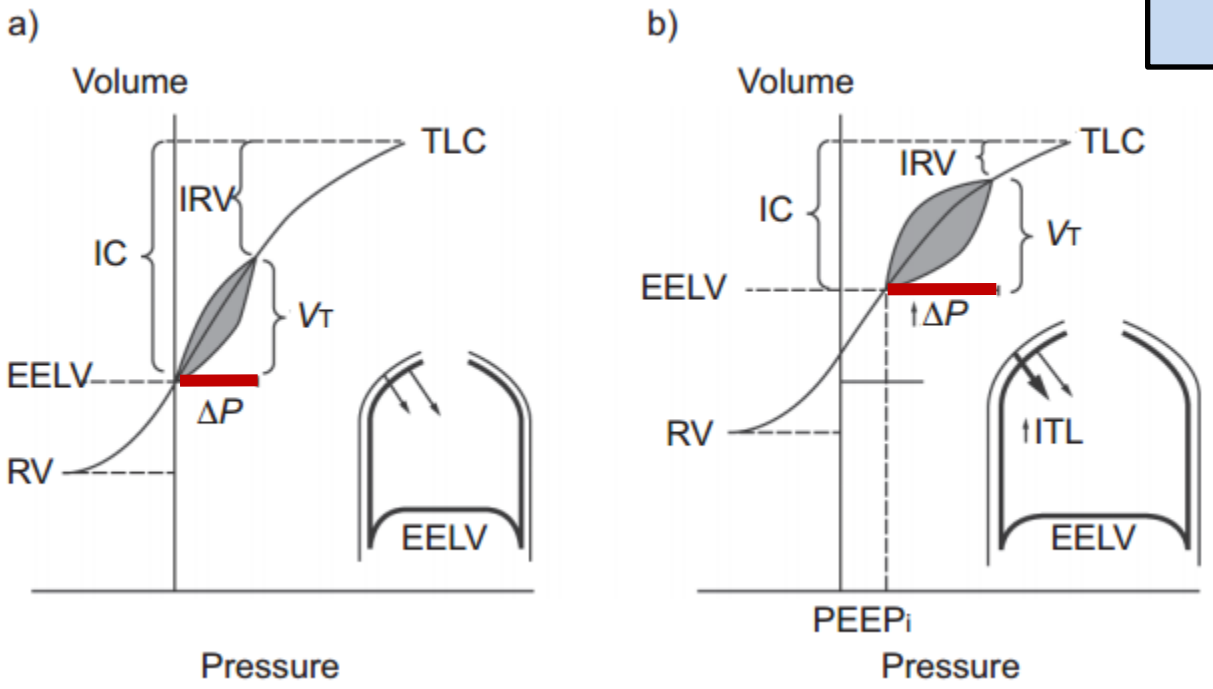


Tashkin et al. NEJM 2008

Anti-inflammatory effects of bronchodilators?

Stable COPD

Exacerbated COPD



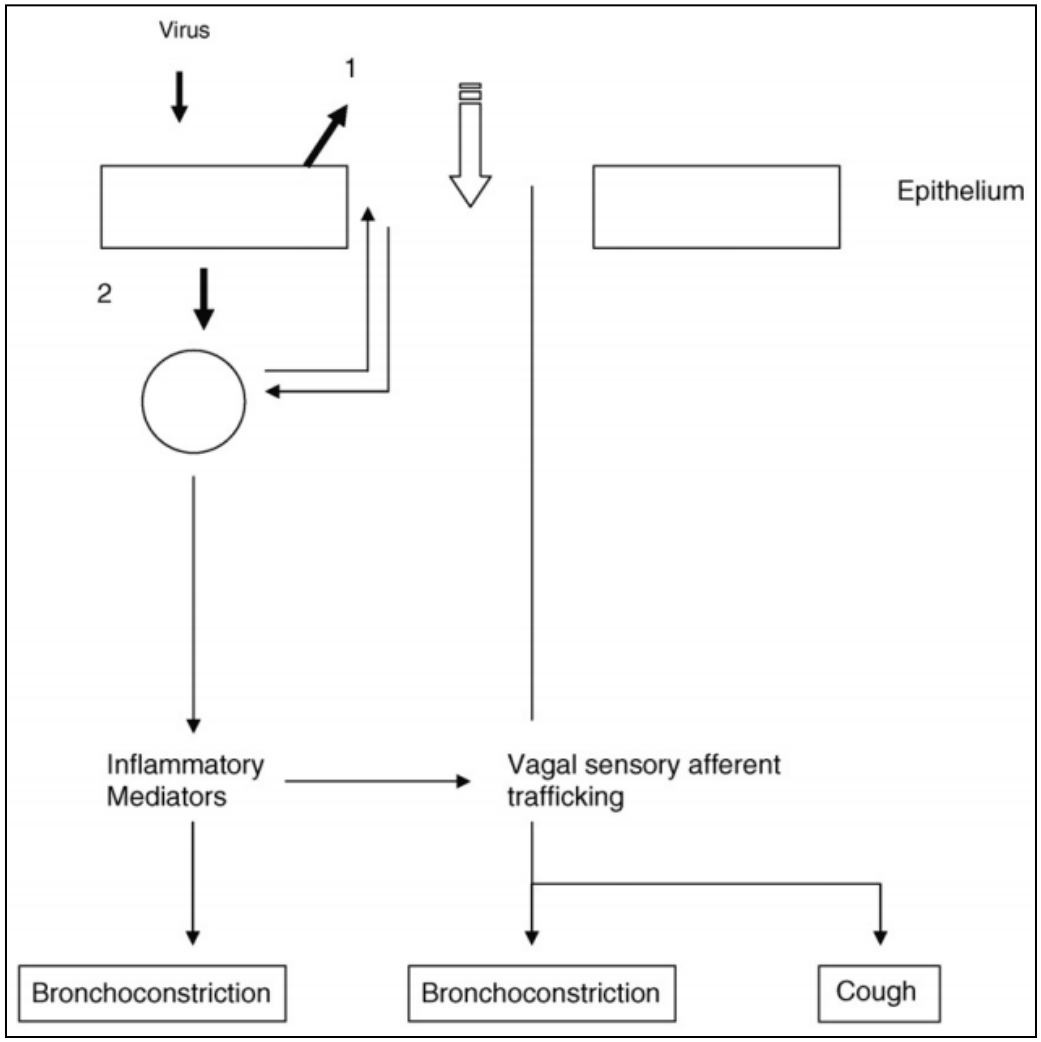
Improvement in airflow obstruction air trapping hyperinflation

Dyspnea ↓
Exercise performance ↑
Ventilation/perfusion imbalance ↓

Cope better with pathophysiological impact of factors such as infections

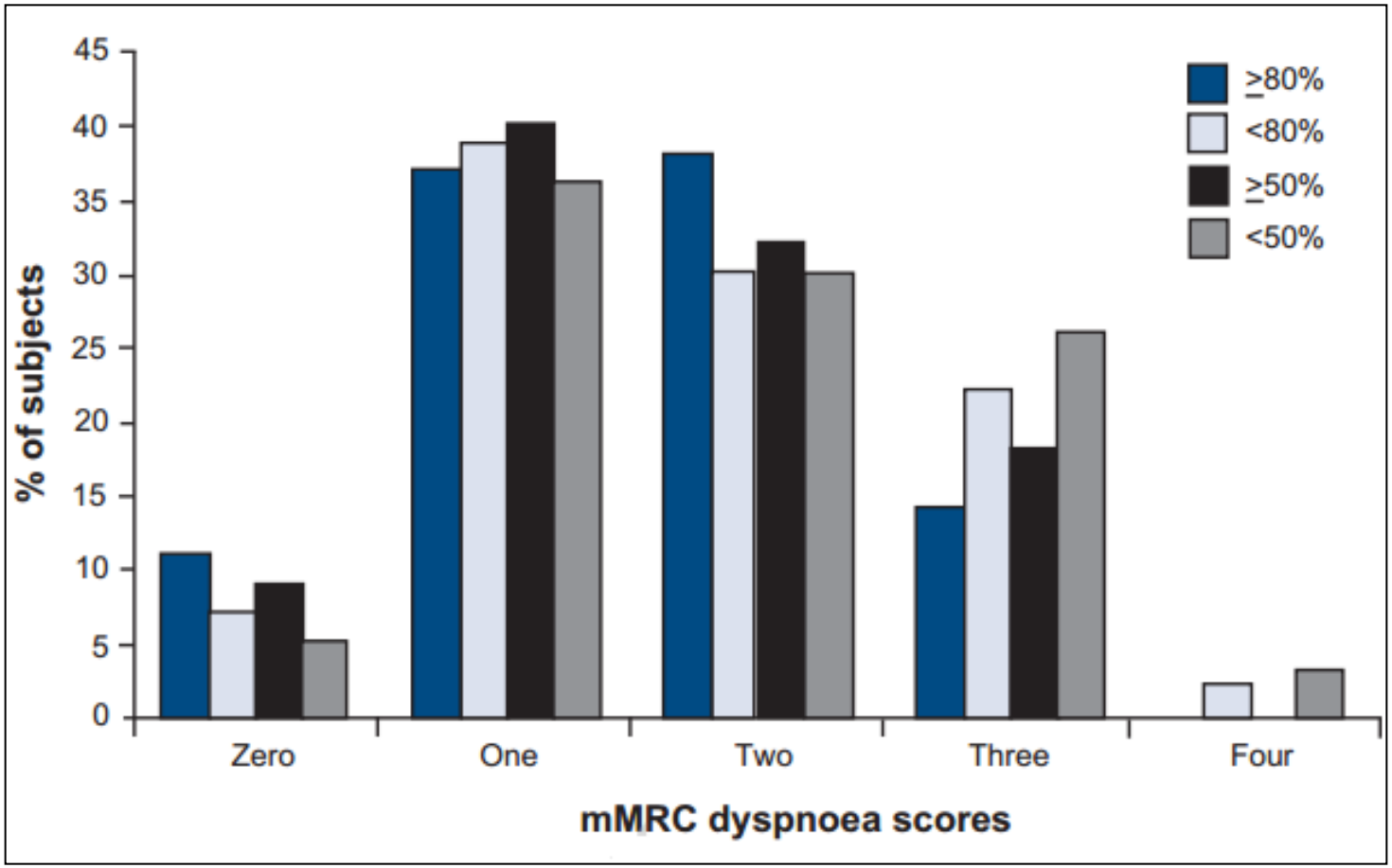
Wedzicha et al. Eur Respir J 2012

Inhibition of viral-induced exacerbation by bronchodilator



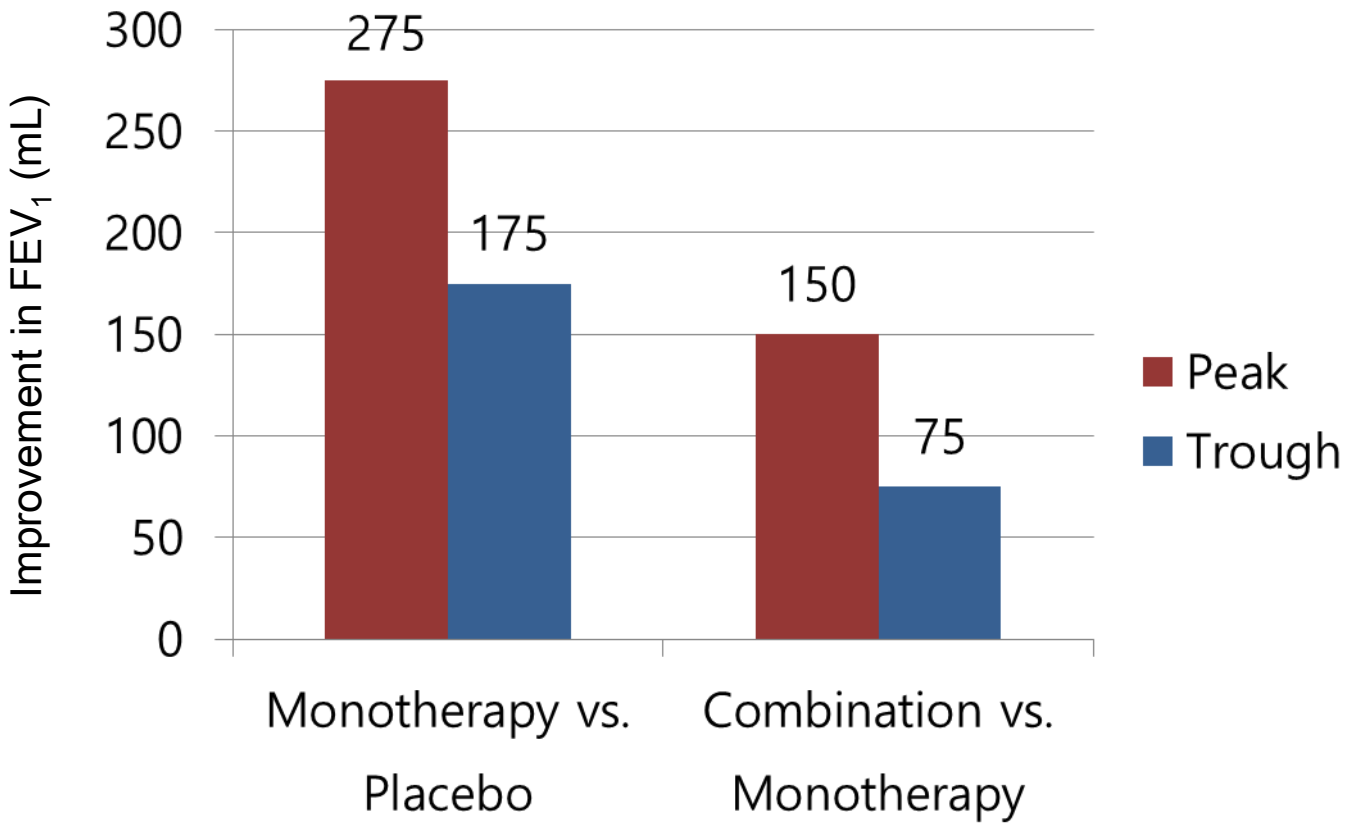
Trevethick et al. Curr Opin Pharmacol 2009

mMRC dyspnea scores in COPD with mono-bronchodilator therapy



Dransfield et al. Prim Care Respir J 2011

Improvement in FEV_1 (mL) with bronchodilator

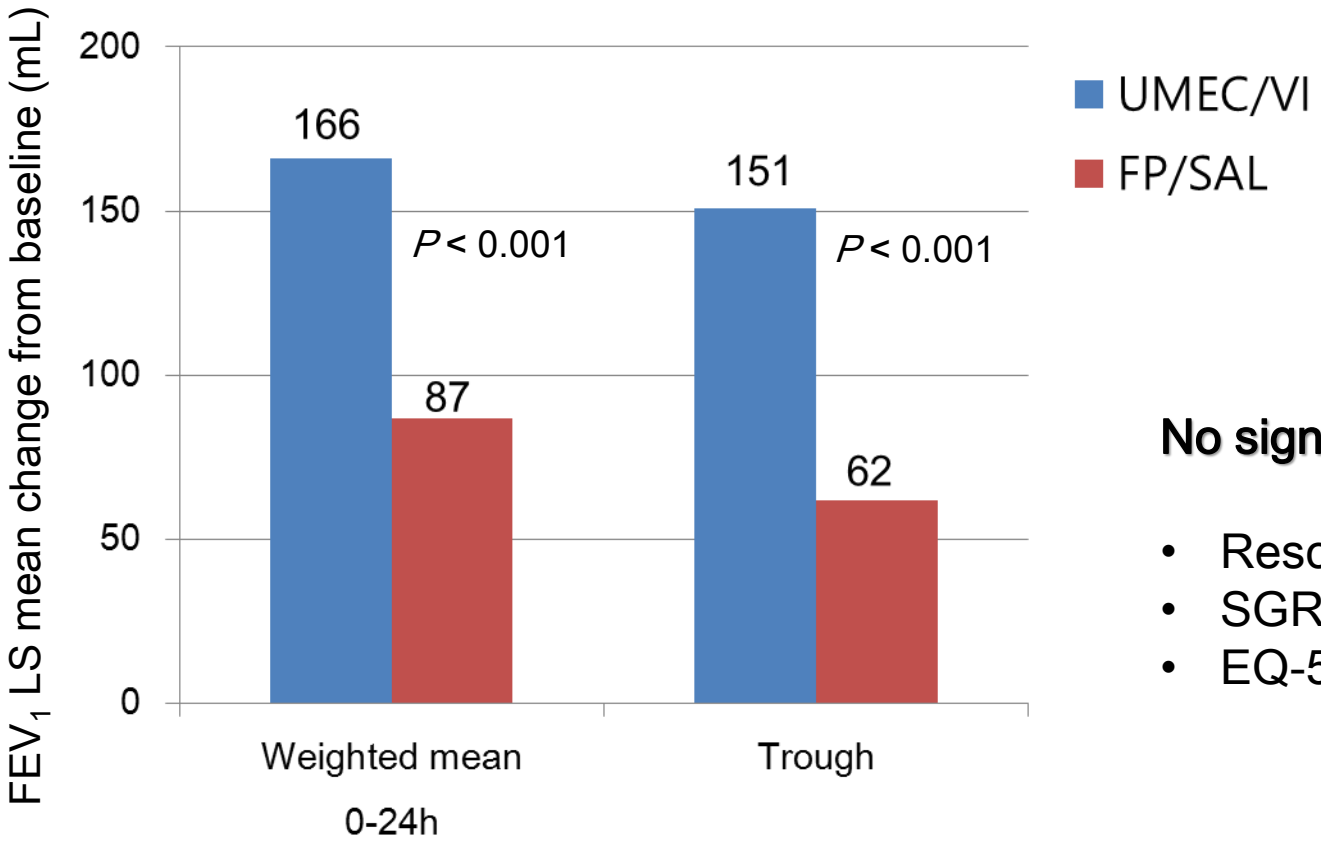


Singh D et al. Br J clin Pharmacol 2015
Singh D et al. BMC Pulm Med 2014
Bateman ED et al. Eur Respir J 2013

LAMA/LABA vs. ICS/LABA in mod/severe COPD

Inclusion: 30% ≤ FEV_1 ≤ 70% pred (B:55%, D:45%), mMRC ≥ 2, no COPD AE
- Umeclidium/vilanterol 62.5/25ug (n=334)
- Fluticasone/salmeterol 500/50ug (n=340)

Duration: 12 wks



No significant difference

- Rescue tx
- SGRQ
- EQ-5D

Singh et al. BMC Pulm Med 2015

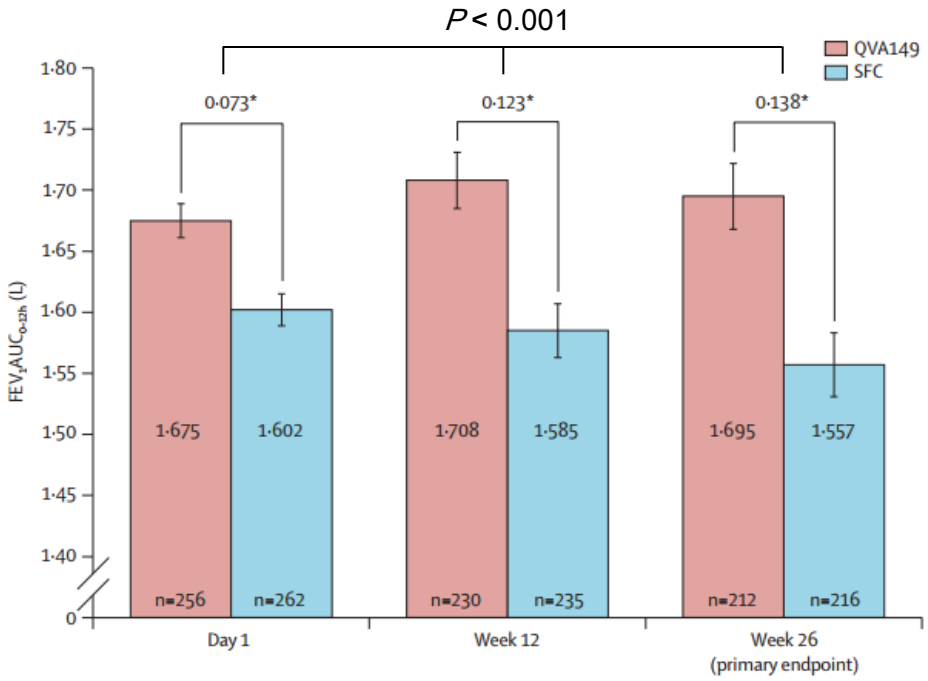
LAMA/LABA vs. ICS/LABA in mod/severe COPD

Inclusion: 40% ≤ FEV_1 ≤ 80% pred (mean 60%), mMRC ≥ 2, no COPD AE

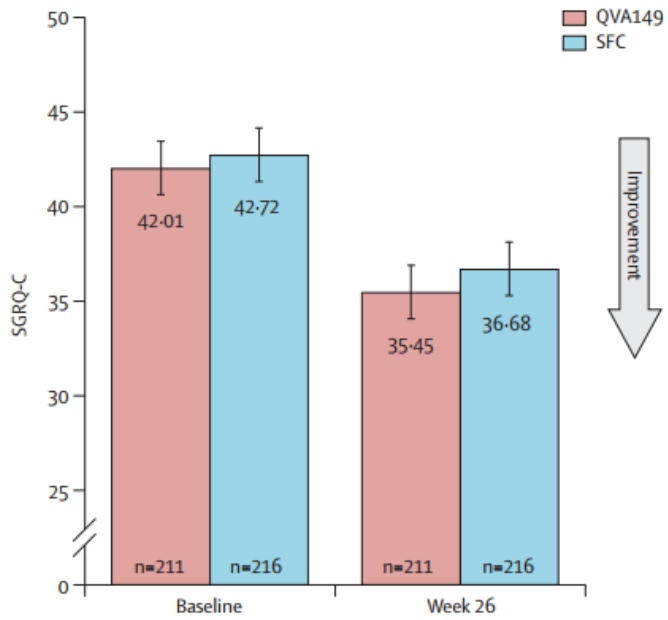
- Indacaterol/glycopyrronium 110/50ug (n=258)
- Fluticasone/salmeterol 500/50ug (n=264)

Duration: 26 wks

FEV_1 AUC_{0-12h}



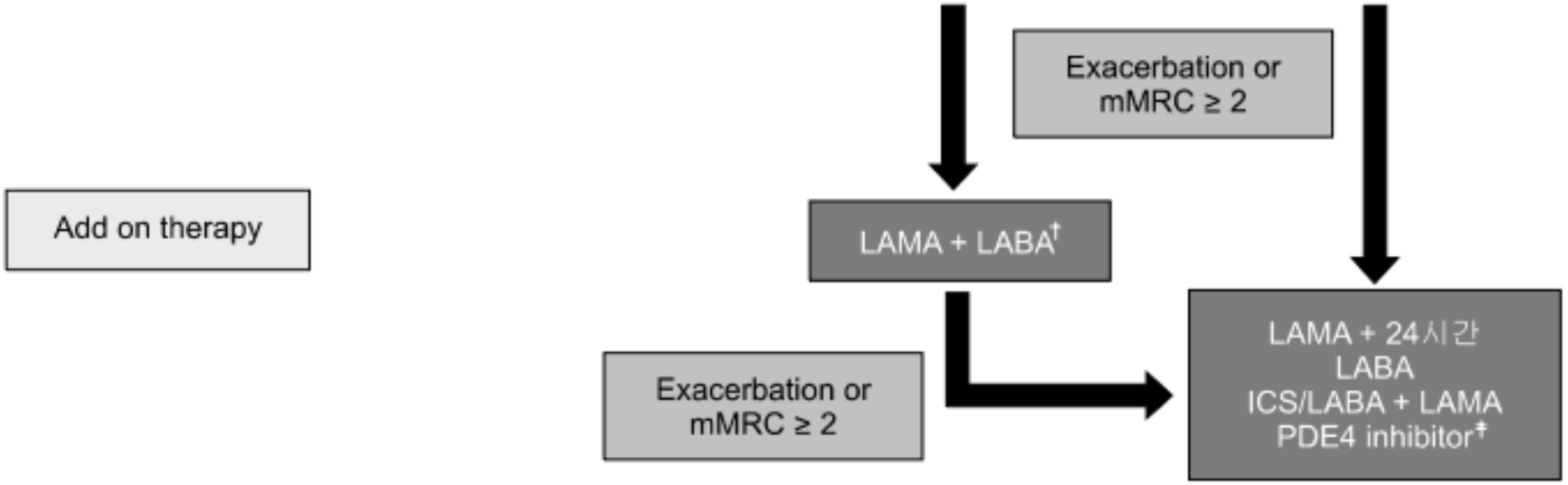
SGRQ



Vogelmeier et al. Lancet Respir Med 2013

Initial Pharmacological Treatment

	$FEV_1 \geq 60\%$ pred. and 0~1 exacerbation/year		$FEV_1 < 60\%$ pred. or ≥ 2 exacerbation/year or history of AE COPD* related admission (다군)
	mMRC 0~1 or CAT < 10 (가군)	mMRC ≥ 2 or CAT ≥ 10 (나군)	
	Short-acting beta2-agnoist as required		
First choice	Short-acting beta2-agnoist as required	LAMA or LABA†	LAMA or 24시간 LABA or ICS/LABA or LABA + LAMA



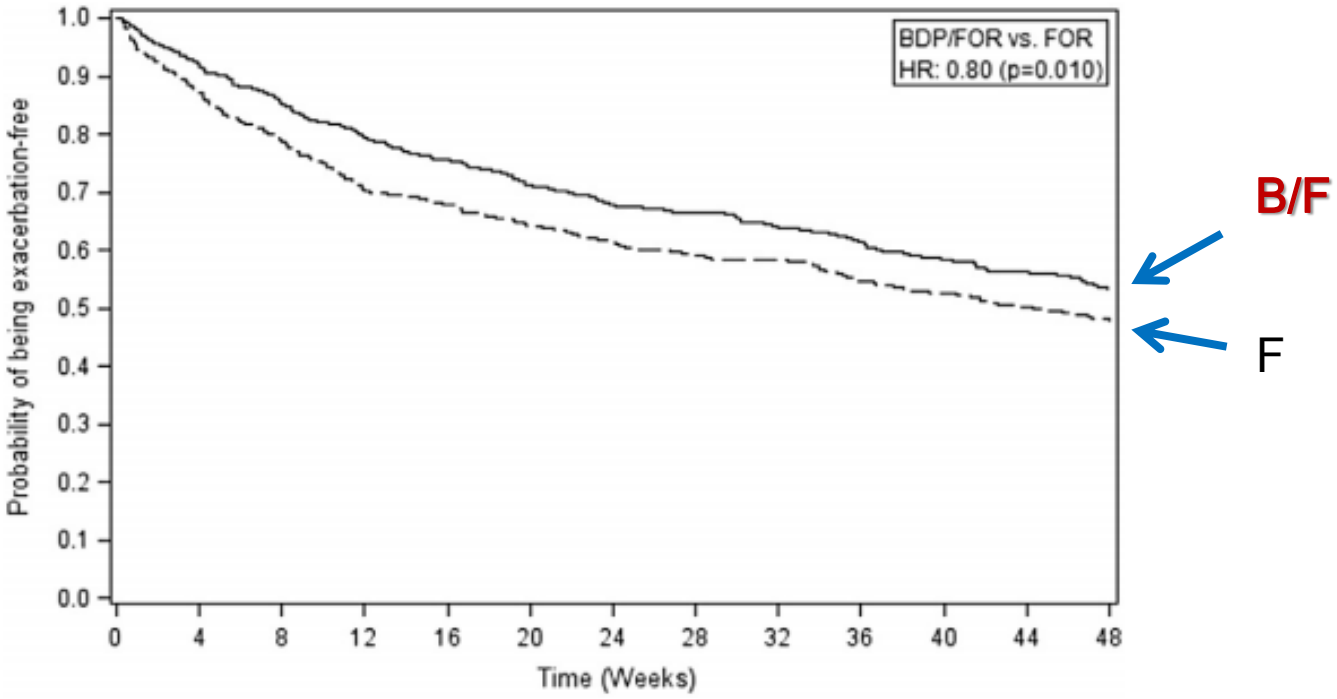
국내 진료 지침 2014

ICS/LABA vs LABA

Inclusion: 30% ≤ FEV_1 < 50% pred, ≥ 1 COPD AE

- Beclomethasone/formoterol 100/6 ug (n=595): 2 inhalations BID
- Formoterol 9ug (n=595): 1 inhalation BID

Duration: 1yr

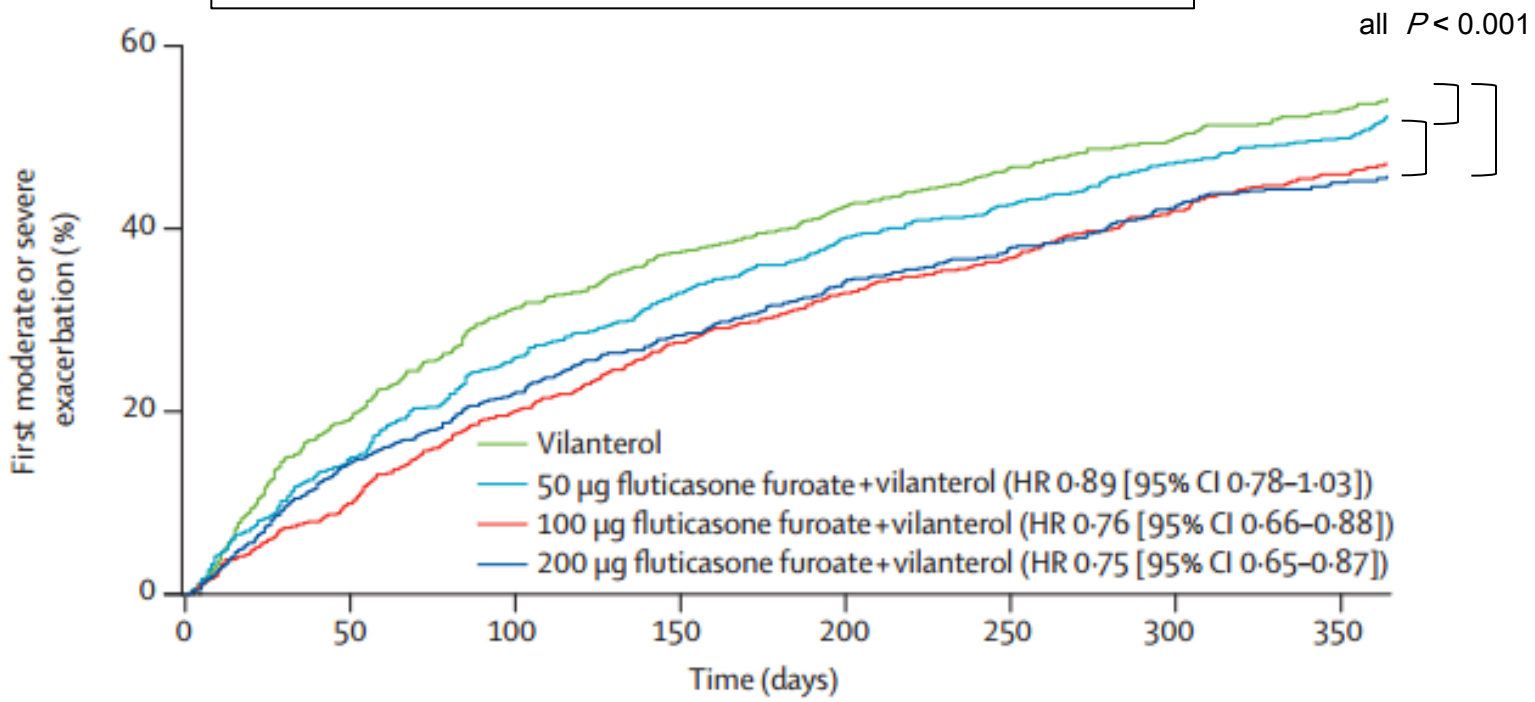


Wedzicha et al. Respir Med 2014

ICS/LABA vs LABA

Inclusion: FEV_1 ≤ 70% pred, ≥ 1 COPD AE
- Fluticasone/vilanterol 50/25ug (n=315)
- Fluticasone/vilanterol 100/25ug (n=312)
- Fluticasone/vilanterol 200/25ug (n=301)
- Vilanterol (n=294)

Duration: 1yr



Dransfield et al. Lancet Respir Med 2013

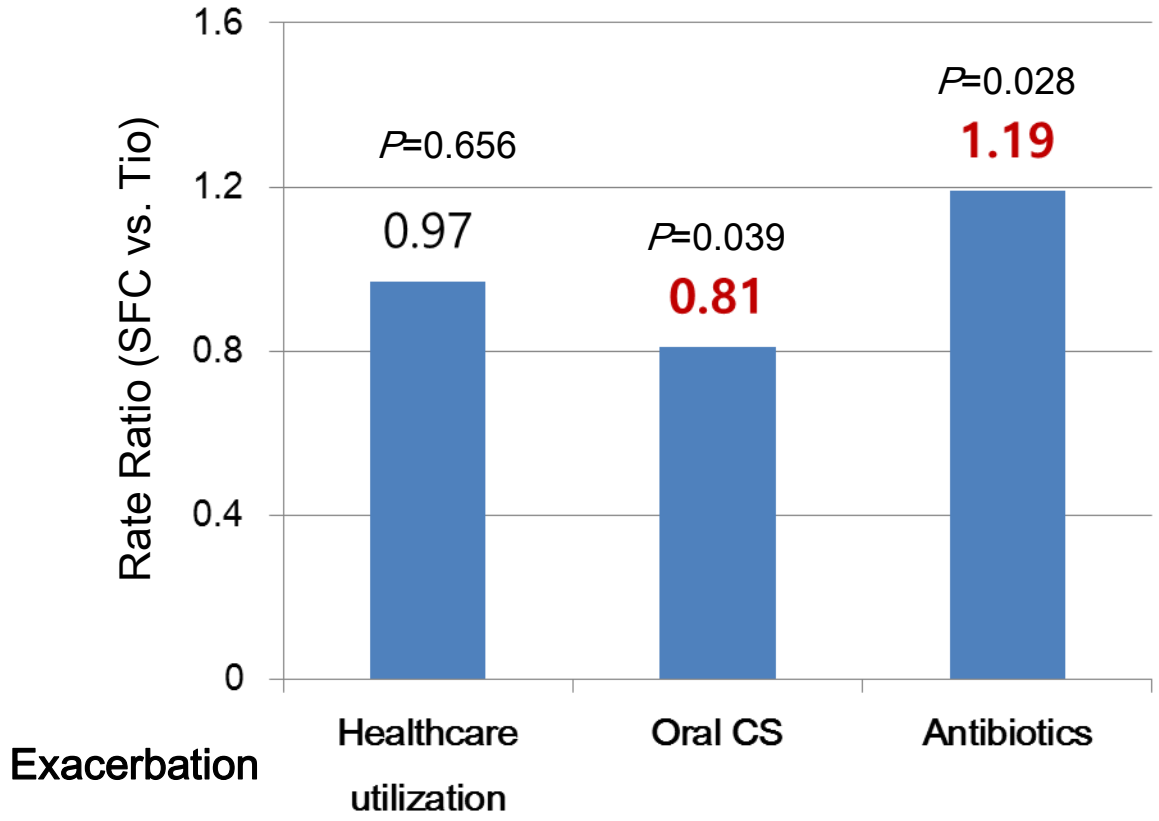
INSPIRE

ICS/LABA vs LAMA

Inclusion: FEV_1 ≤ 50% pred, ≥ 2 mMRC, COPD AE (85% ≥ 1)

- Fluticasone/salmeterol 500/50ug (n=658)
- Tiotropium 18ug (n=665)

Duration: 2 yrs



Wedzicha et al. Am J Respir Crit Care Med 2008

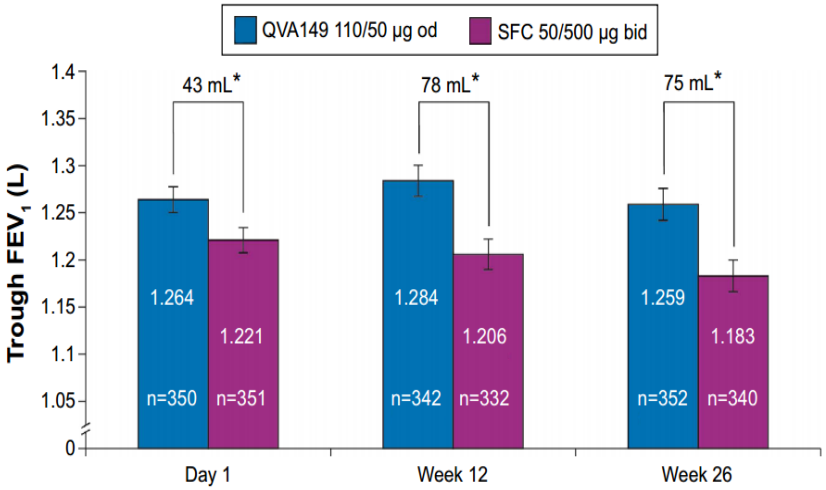
LANTERN

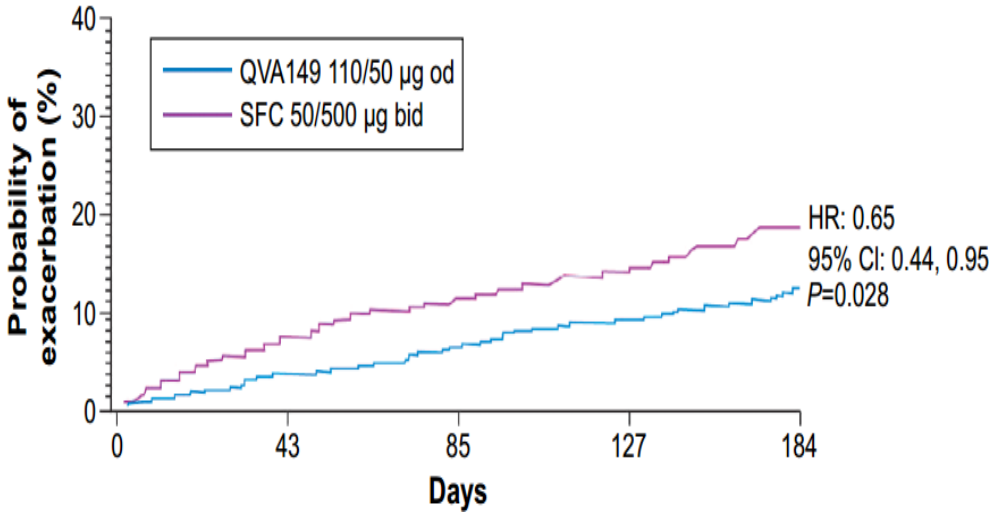
ICS/LABA vs LABA/LAMA

Inclusion: : 30% ≤ FEV_1 < 80% pred (B 52%, D47%), ≥ 2 mMRC, ≤ 1 COPD AE

- Indacaterol/glycopyrronium 110/50ug (n=343)
- Fluticasone/salmeterol 500/50ug (n=333)

Duration: 26wks





Zhong et al. Int Jr COPD 2015

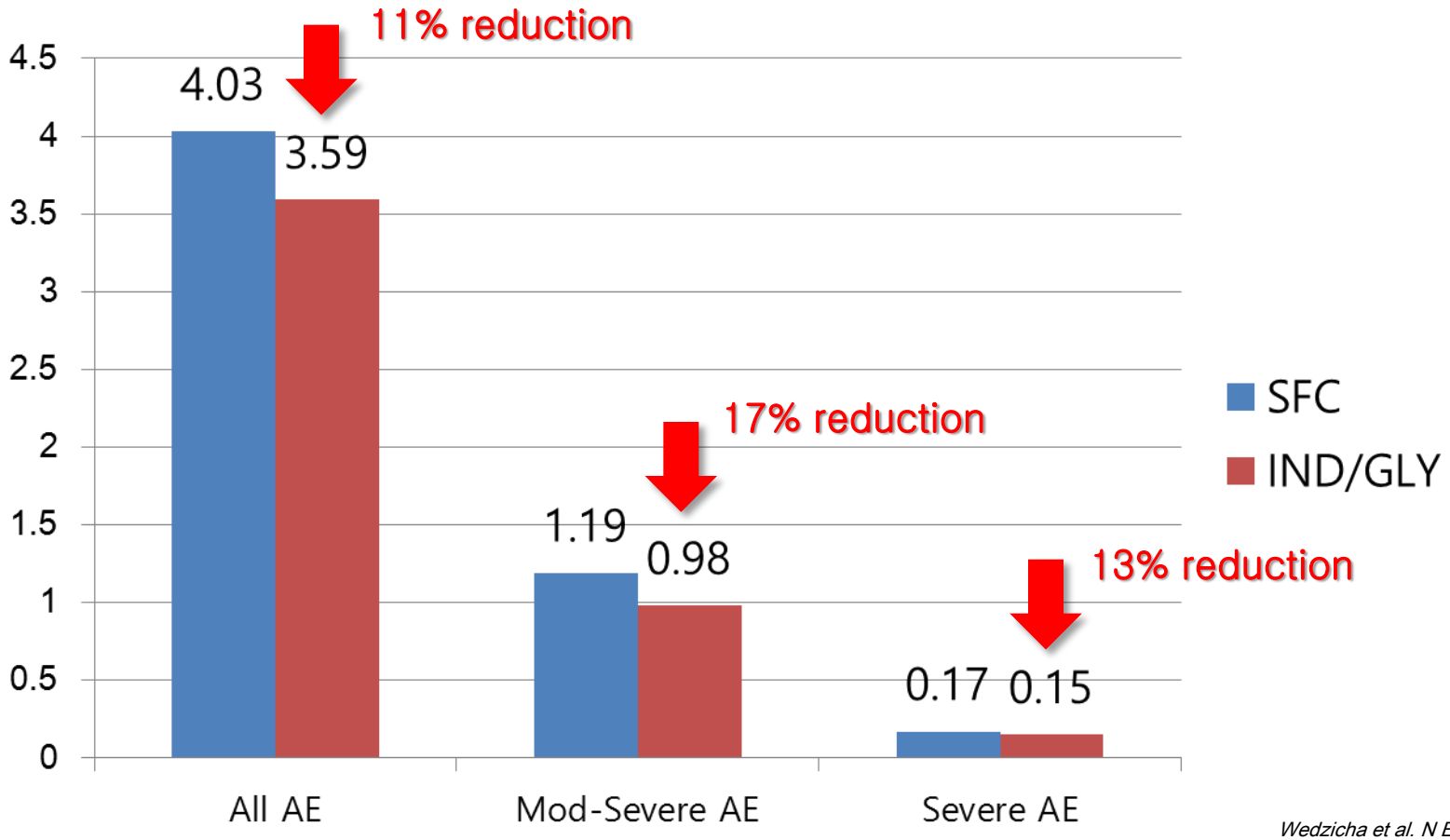
FLAME

ICS/LABA vs LABA/LAMA

Inclusion: : 25% ≤ FEV_1 < 60% pred, ≥ 2 mMRC, ≥ 1 COPD AE

- Indacaterol/glycopyrronium 110/50ug (n=1400)
- Fluticasone/salmeterol 500/50ug (n=1360)

Duration: 1yr



Wedzicha et al. N Eng Jr Med 2016

Salford Lung Study

ICS/LABA vs usual care

Inclusion: documented diagnosis of COPD from general practitioner, ≥ 1 COPD AE in 3 yrs

- Fluticasone/vilanterol 100/25 ug (n=1396): triple → with LAMA (+)
- Usual care (n=1403)

Duration: 1yr

	Entire Population	Usual care	FF/VI
COPD severity			
0	268 (12)	136 (12)	132 (12)
1-2	1293 (59)	641 (58)	652 (59)
3-4	638 (29)	324 (29)	314 (29)
Pre-randomization COPD therapy			
LA-bronchodilator alone or combi	391 (14)	196 (14)	195 (14)
ICS alone ± with a LA bronchodilator	958 (34)	480 (34)	478 (34)
Triple therapy	1450 (52)	727 (52)	723 (52)

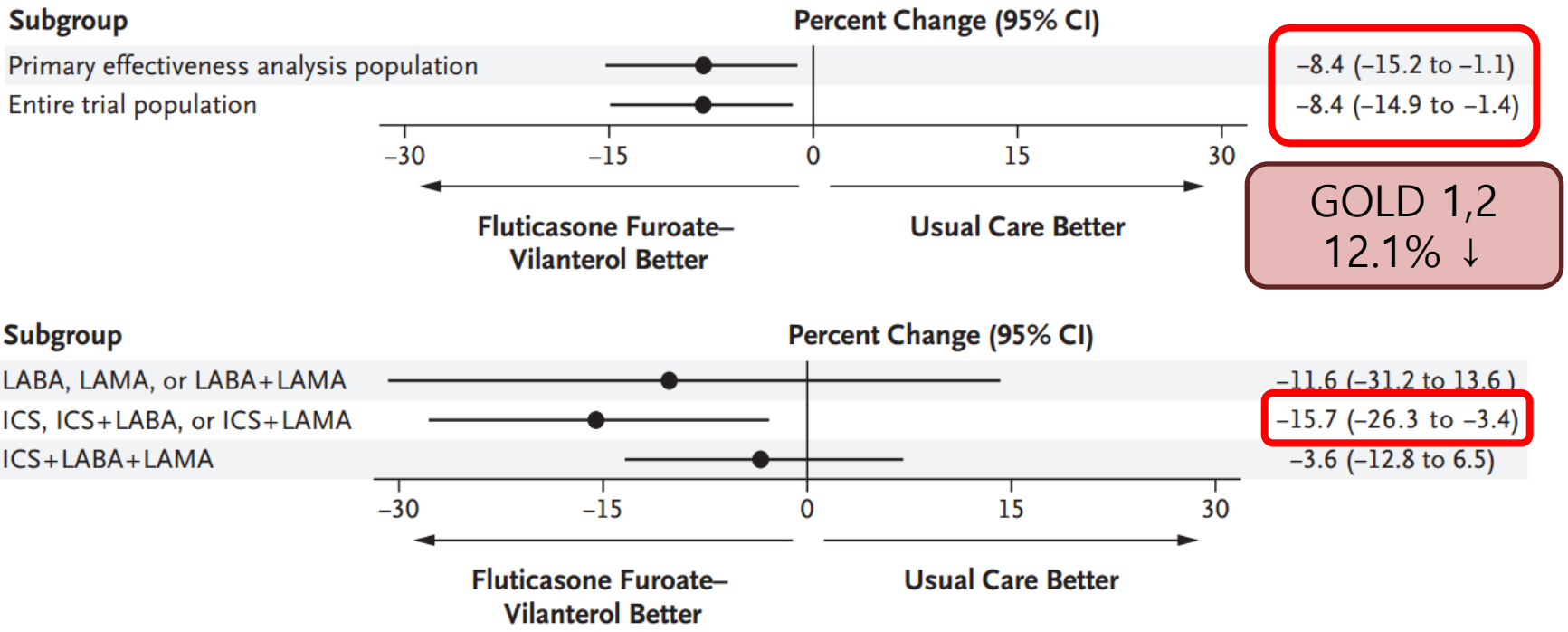
LA: long acting

Vestbo et al. NEJM 2016

Salford Lung Study

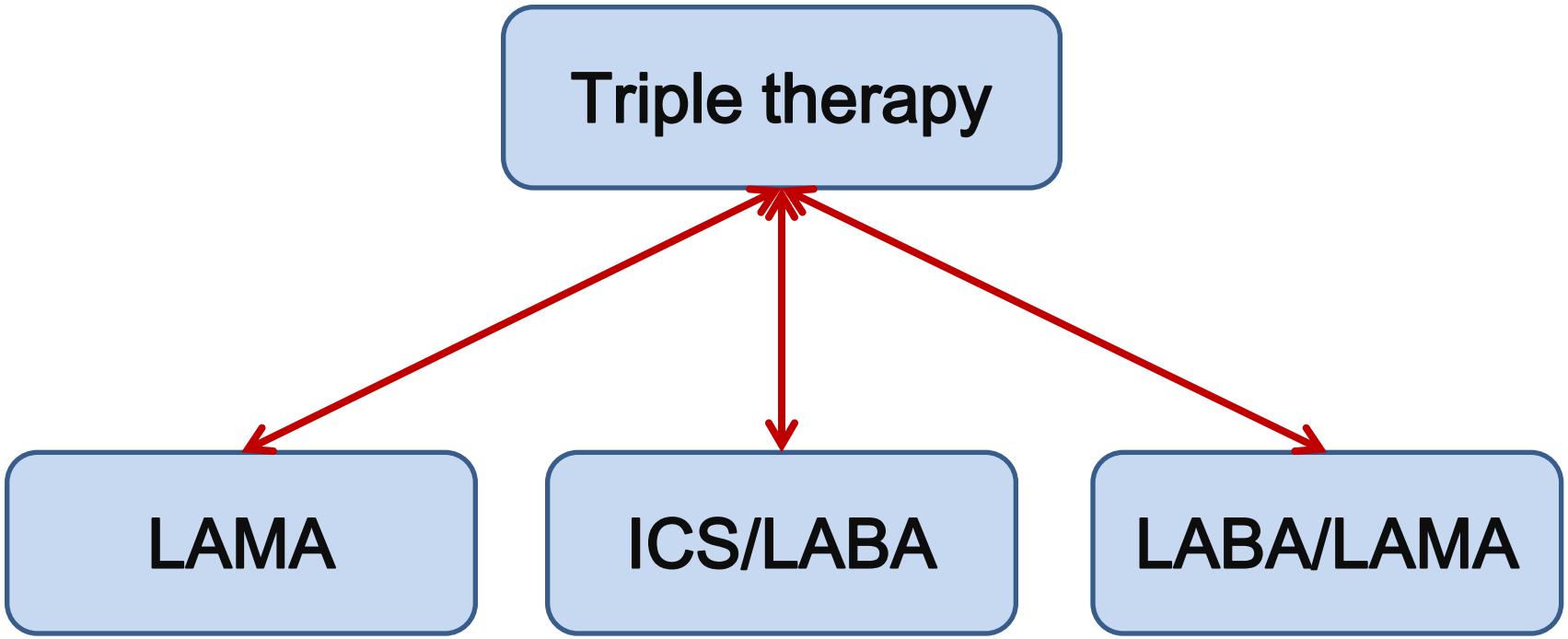
ICS/LABA vs usual care

Moderate or Severe Exacerbations

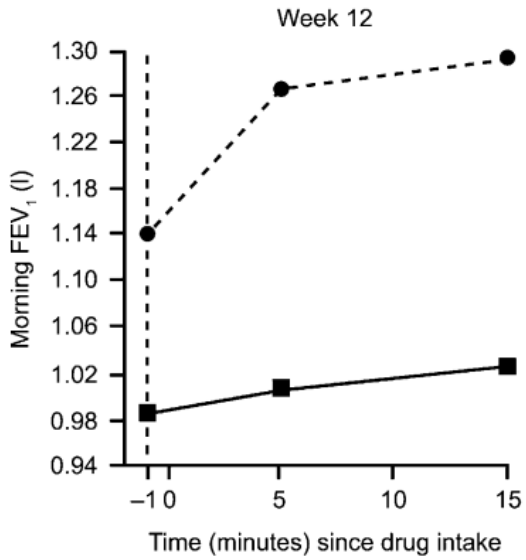


Vestbo et al. NEJM 2016

Triple Combination Therapy



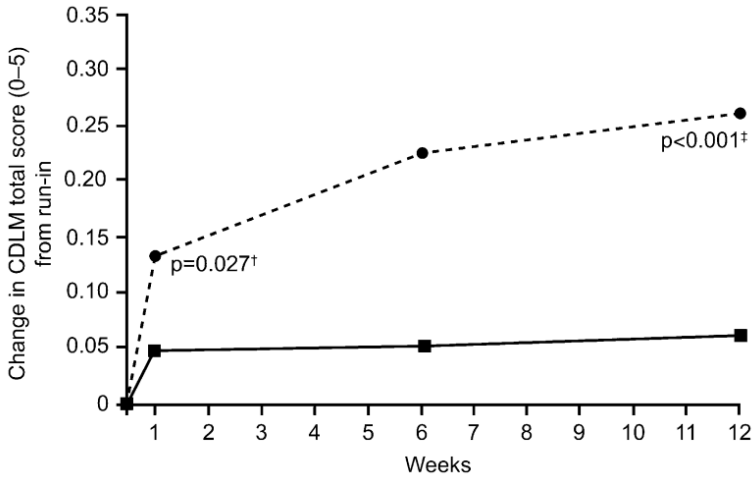
Triple therapy vs LAMA

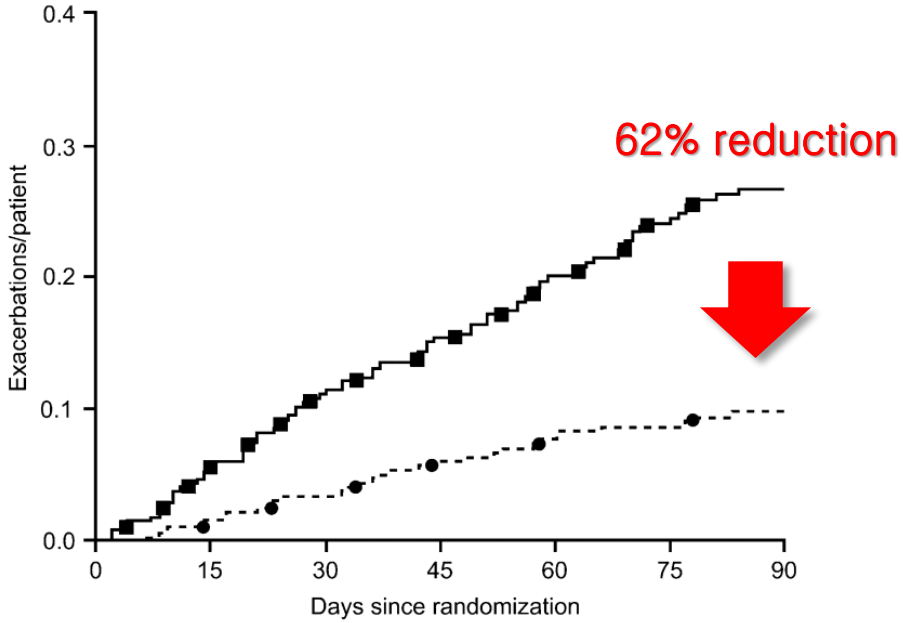


Inclusion: FEV_1 < 65% pred

- Tiotropium/budesonide/formoterol 18/320/9 ug (n=302)
- Tiotropium 18ug (n=303)

Duration: 12wks





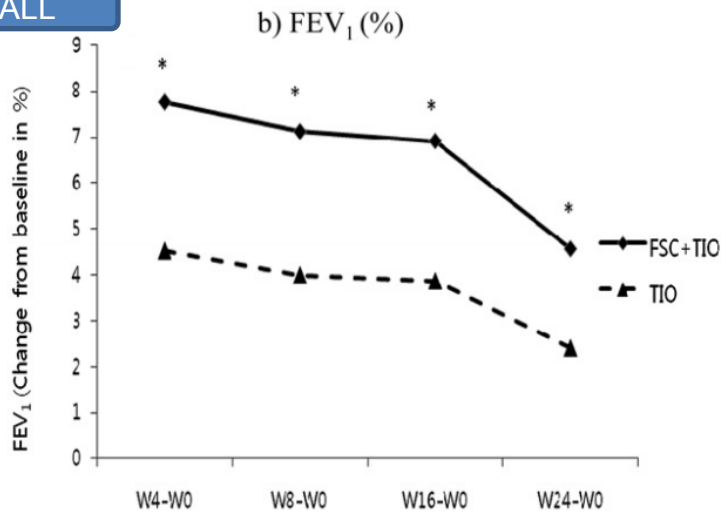
CDLM: Capacity of Daily Living during the Morning questionnaire

Welte et al. Am J Respir Crit Care Med 2009

SUPER

Triple therapy vs LAMA

ALL

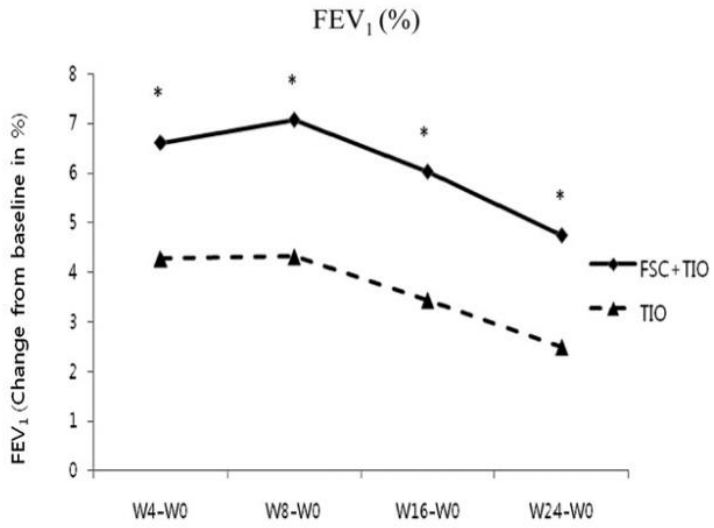


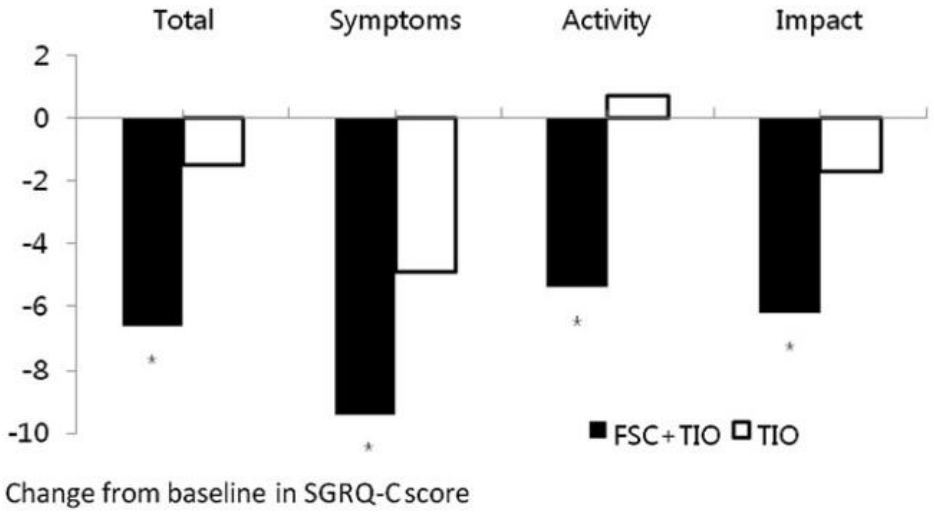
Inclusion: FEV_1 < 65% pred

- Tiotropium/fluticasone/salmeterol 18/250/50 ug (n=206)
- Tiotropium 18ug (n=209)

Duration: 24wks

50% < FEV_1 ≤ 65% pred





Jung et al. Respi Med 2012

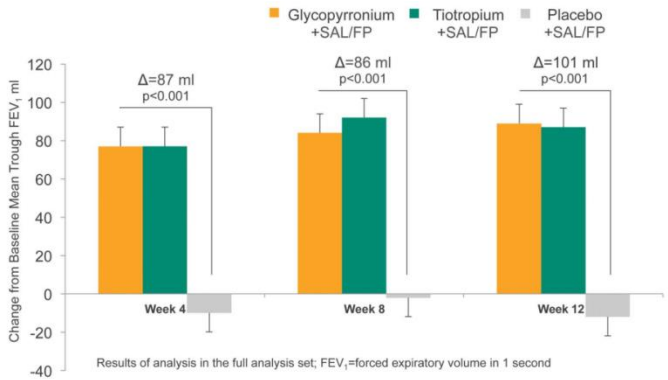
GLISTEN

Triple therapy vs ICS/LABA

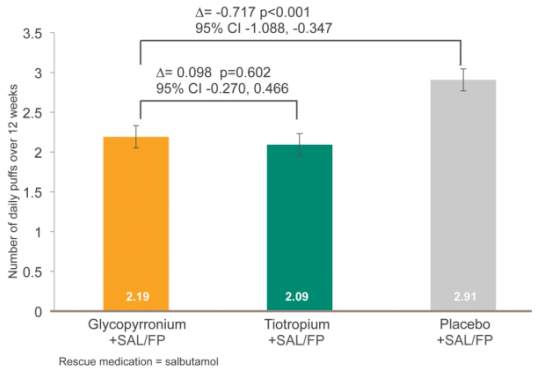
Inclusion: 30% ≤ FEV_1 < 80% pred
- Glycopyrronium/ fluticasone/salmeterol 50/500/50ug (n=229)
- Tioropium/fluticasone/salmeterol 18/500/50ug (n=226)
- Placebo/fluticasone/salmeterol 500/50ug (n=201)

Duration: 12wks

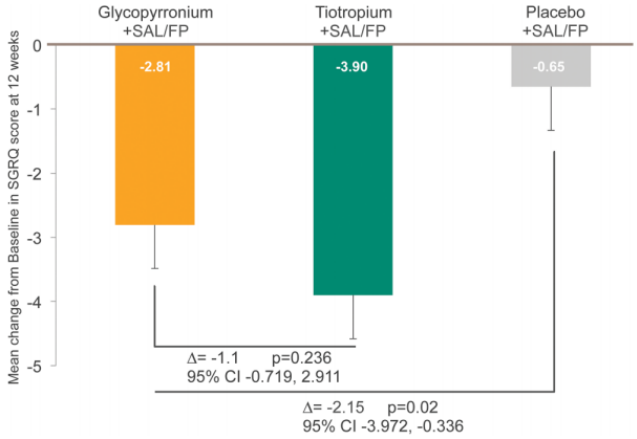
Change from baseline mean trough FEV_1



Number of daily puffs



SGRQ



Exacerbation: no difference

Frith et al. Thorax 2015

TRIOLOGY

Triple therapy vs ICS/LABA

Inclusion: FEV_1 < 50% pred, ≥ 1 COPD AE

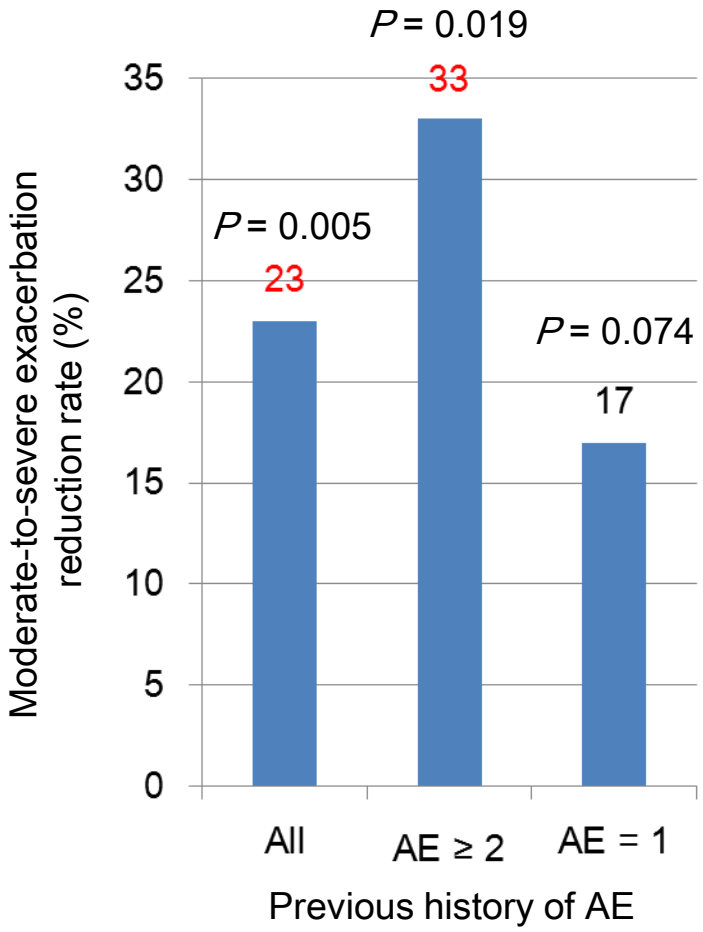
- Beclomethasone/formoterol 100/6 ug (n=579): 2 inhalations BID
- Beclomethasone/formoterol/glycopyrronium 100/6/12.5ug (n=602):2 inh BID
- Duration: 1yr

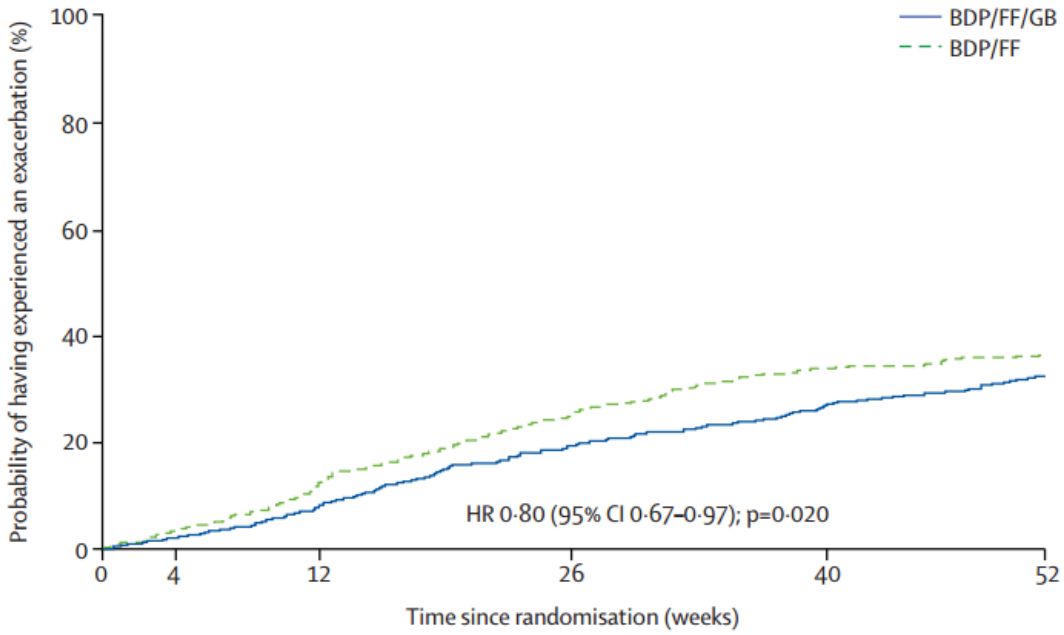
	BDP/FF/GB (N=687)	BDP/FF (N=680)	Odds ratio	p value
Pre-dose FEV_1 (≥100 mL increase from baseline)				
Week 26	287 (42%)	165 (24%)	2·30 (1·82–2·91)	p<0·001
Week 52	259 (38%)	158 (23%)	2·06 (1·62–2·62)	p<0·001
TDI (focal score ≥1)				
Week 26	394 (57%)	352 (52%)	1·28 (1·03–1·59)	p=0·027
Week 52	370 (54%)	354 (52%)	1·09 (0·88–1·36)	p=0·430
SGRQ (≥4 unit decrease from baseline in total score)				
Week 26	321 (47%)	246 (36%)	1·52 (1·21–1·91)	p<0·001
Week 52	297 (43%)	244 (36%)	1·33 (1·06–1·66)	p=0·014

Singh et al. Lancet 2016

TRIOLOGY

Triple therapy vs ICS/LABA





Singh et al. Lancet 2016

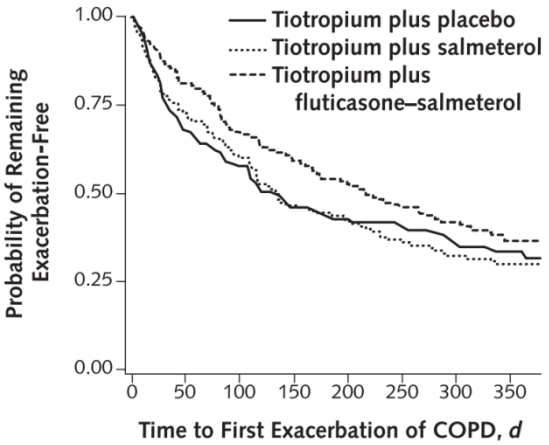
OPTIMAL

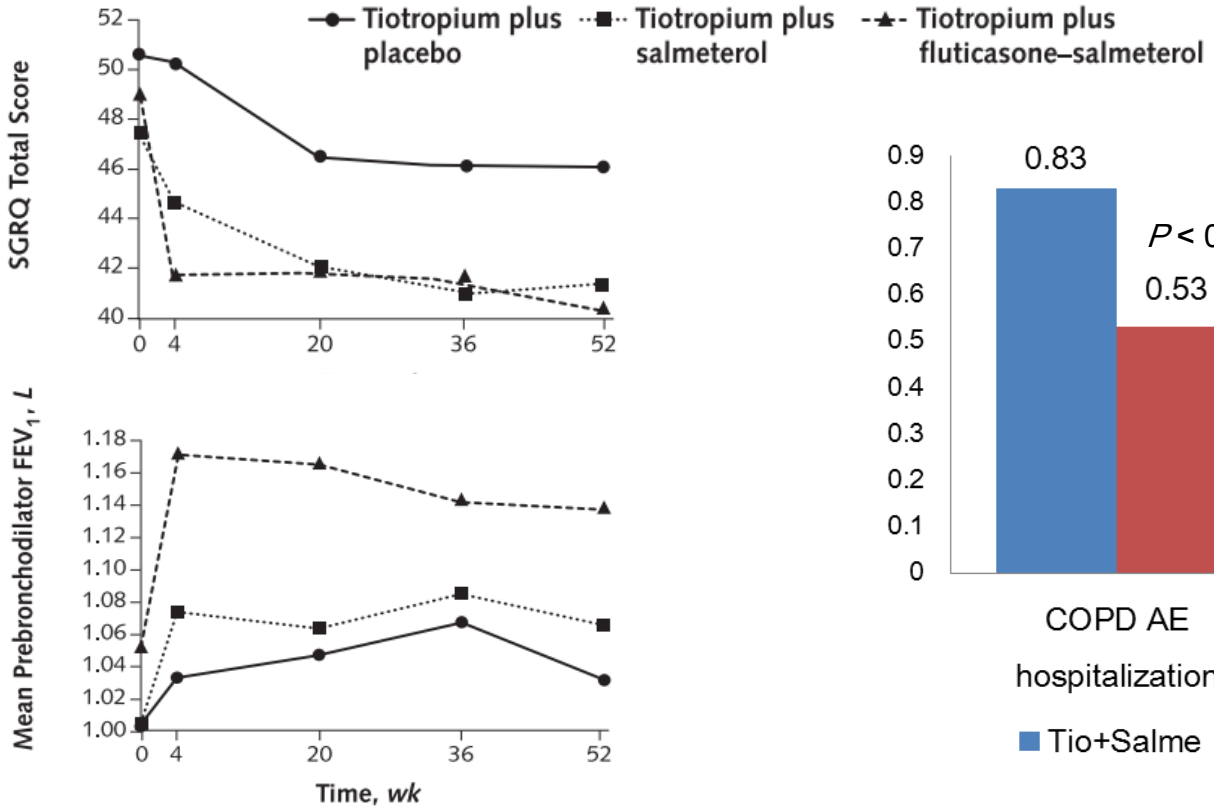
Triple therapy vs LAMA/LABA

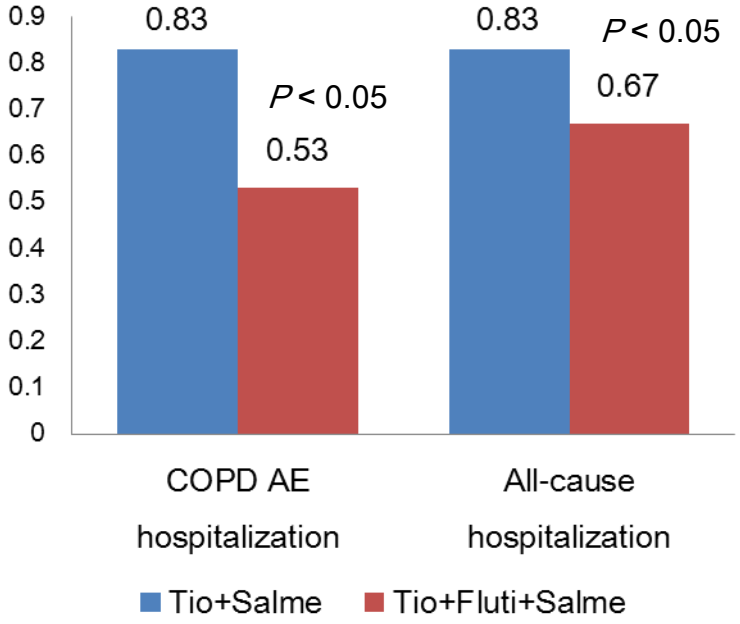
Inclusion: : FEV_1 < 65% pred, ≥ 2 mMRC, ≥ 1 COPD AE

- Tiotropium 18ug (n=156)
- Tiotropium/salmeterol 18/50ug (n=148)
- Tiotropium/fluticasone/salmeterol 18/500/50ug(n=145)

Duration: 1yr







Aaron et al. Iann Int Med 2007

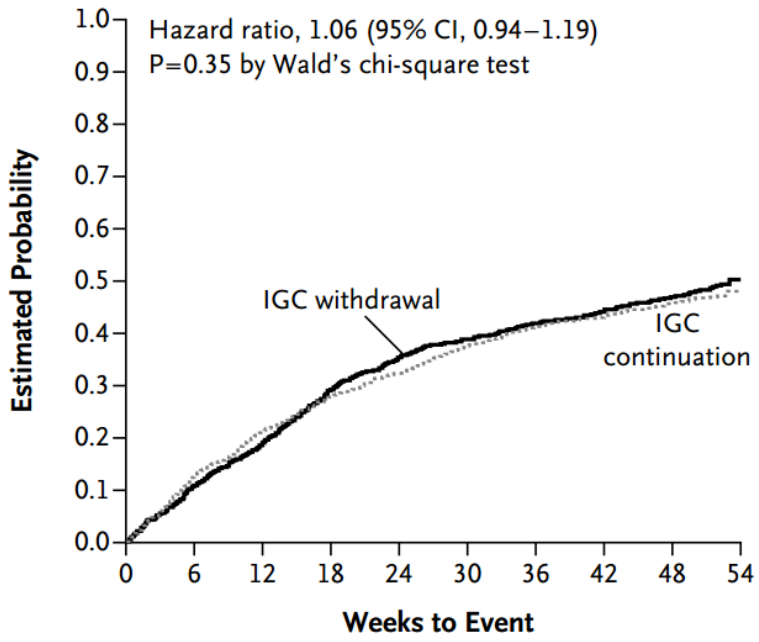
WISDOM

Triple therapy vs LAMA/LABA

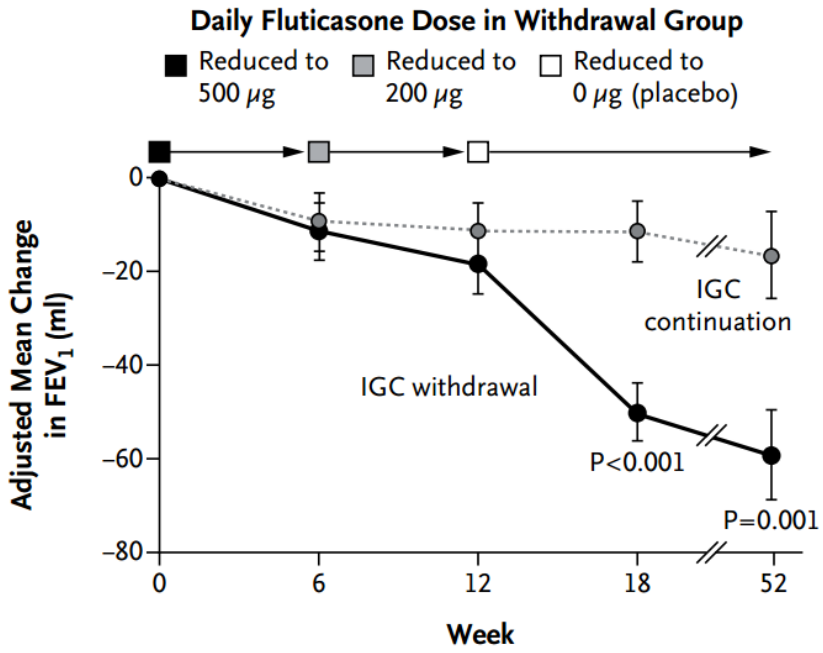
Inclusion: : FEV_1 < 50% pred, ≥ 2 mMRC, ≥ 1 COPD AE
- Tiotropium/fluticasone/salmeterol 18/500/50ug(n=1016)
- Fluticasone withdrawal (12wks) (n=1011)

Duration: 1yr

Moderate or Severe Exacerbation



Change from baseline in trough FEV_1

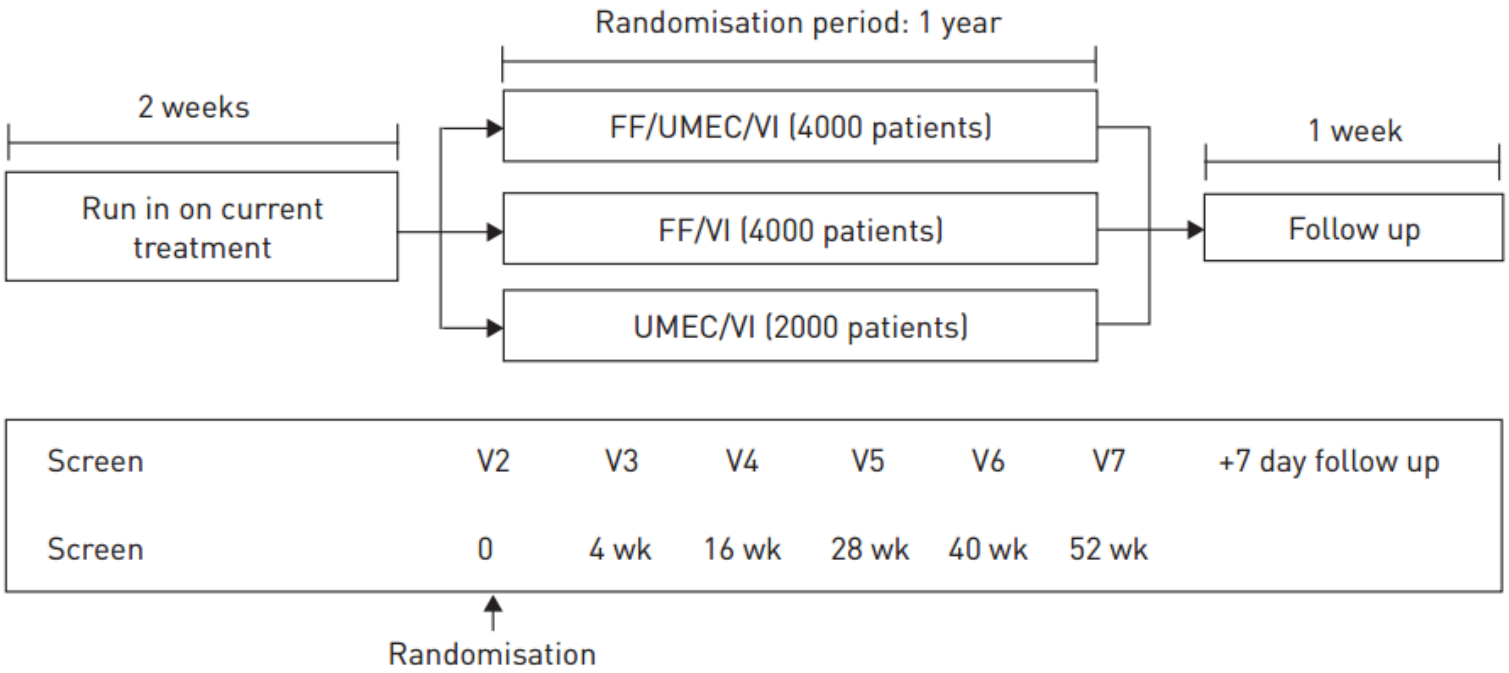


Magnussen H, et al. N Engl J Med 2014

IMPACT

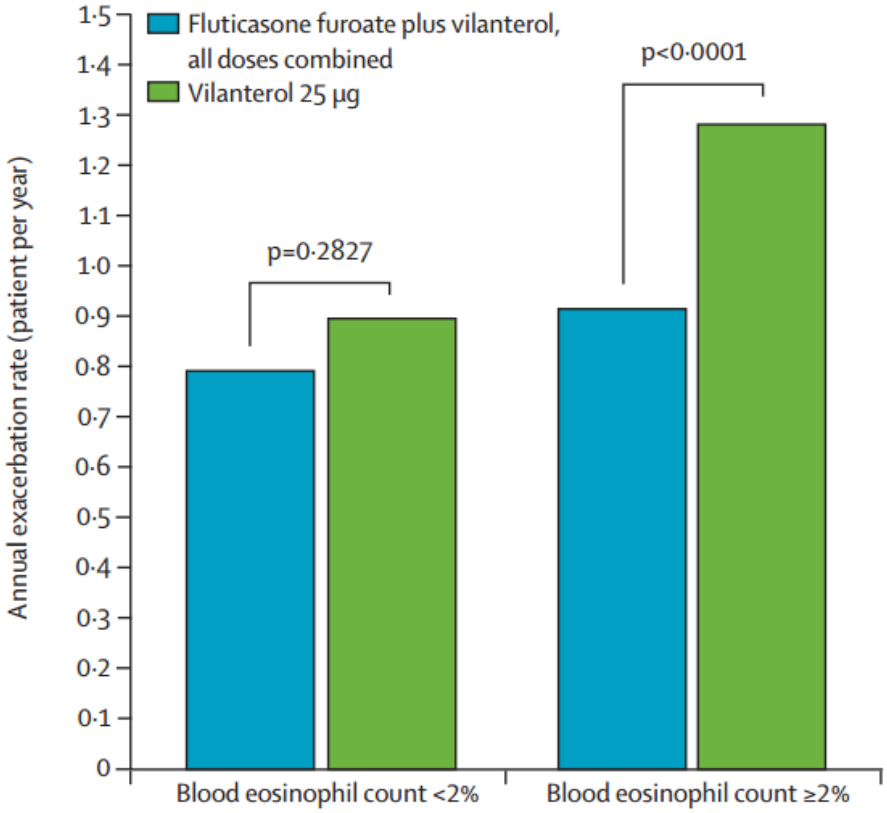
Triple therapy vs LAMA/LABA

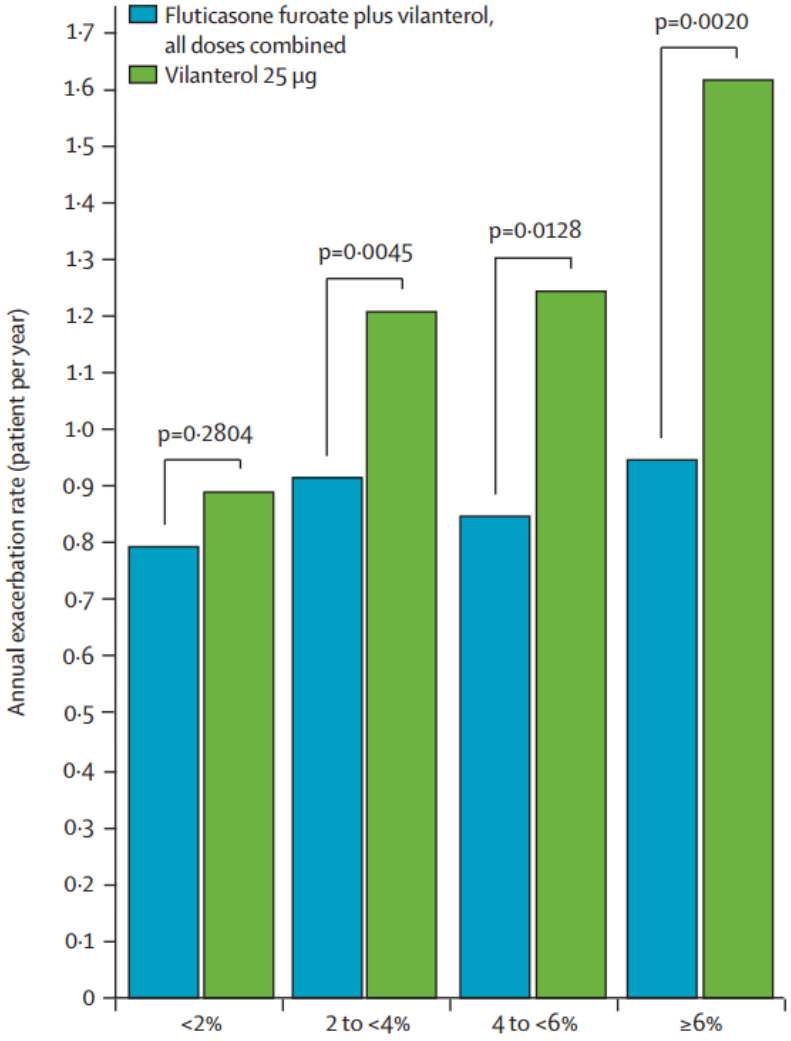
Inclusion: FEV_1 < 50% pred, ≥1 COPD AE; 50% ≤ FEV_1 < 80% pred, ≥2 COPD AE
Duration: 1yr



Pascoe, et al. N Eur Respi Jr 2016

Blood eosinophil counts and Exacerbations





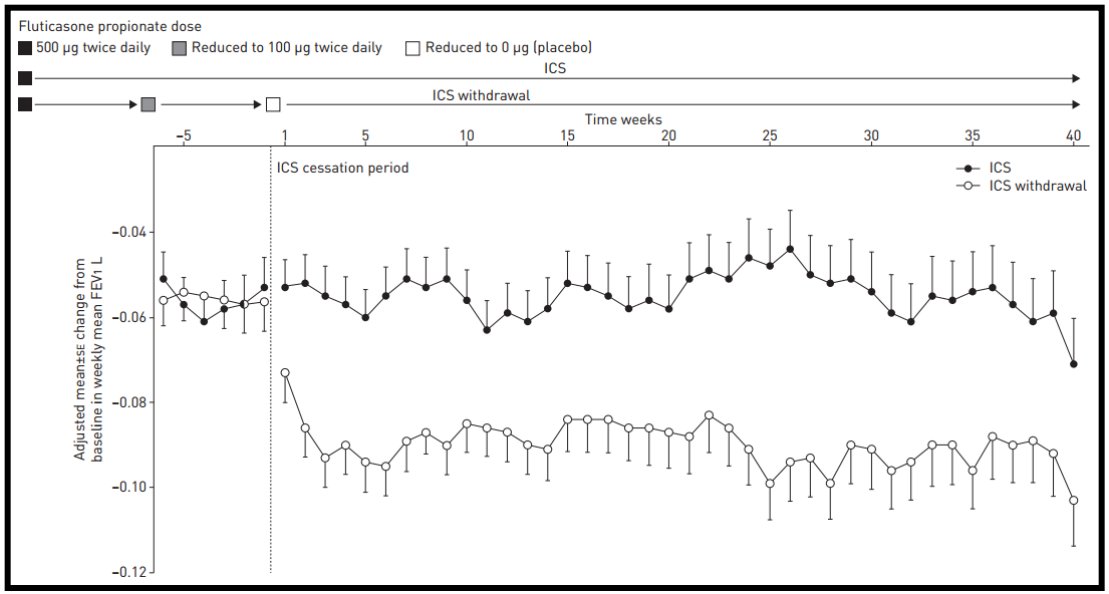
Pascoe et al. Lancet Respir Med 2015

Blood eosinophil counts and Exacerbations

WISDOM

Baseline eosionophils	Exacerbation Rate ratio	*P*-value
≥2%	1.22	0.033
≥3%	1.27	0.053
≥4%	1.63	0.0025
≥5%	1.82	0.0049
≥6%	1.50	0.11
≥150 cells per μL	1.17	0.094
≥300 cells per μL	1.56	0.0055
≥400 cells per μL	1.73	0.009

Lung function changes over time following withdrawal of ICS

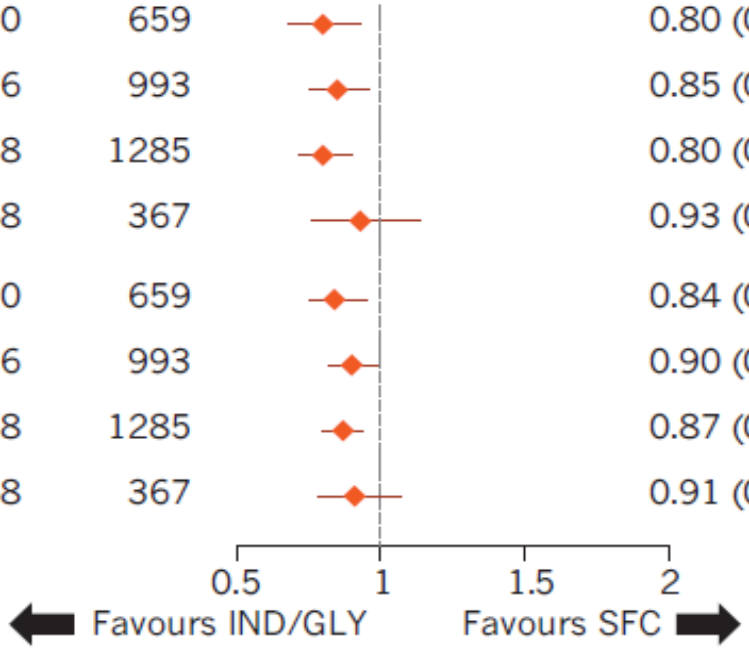


Watz et al. Lancet Respir Med 2016
Magnussen et al. Eur Respir J 2016

COPD exacerbations based on blood eosinophil

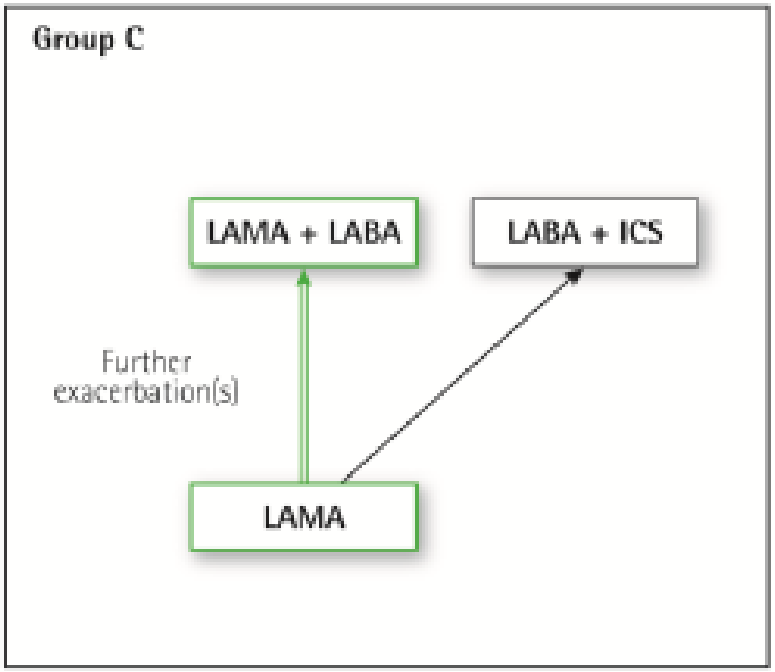
FLAME

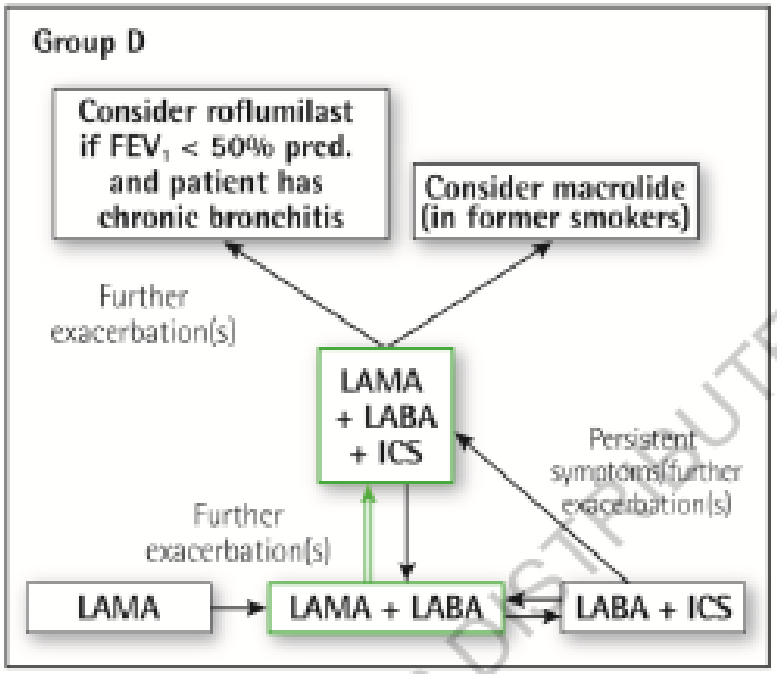
	Blood eosinophil counts	IND/GLY o.d. (n)	SFC b.i.d. (n)	Rate ratio (95% CI)	*P* value
Moderate or severe exacerbations	<2%	620	659	0.80 (0.68 to 0.93)	0.004
	≥2%	1026	993	0.85 (0.75 to 0.96)	0.010
	<300 cells/µL	1278	1285	0.80 (0.72 to 0.90)	< 0.001
22.2%	≥300 cells/µL	368	367	0.93 (0.76 to 1.14)	0.468
Mild/moderate/ severe exacerbations	<2%	620	659	0.84 (0.75 to 0.95)	0.004
	≥2%	1026	993	0.90 (0.82 to 0.99)	0.030
	<300 cells/µL	1278	1285	0.87 (0.80 to 0.94)	< 0.001
	≥300 cells/µL	368	367	0.91 (0.78 to 1.07)	0.249

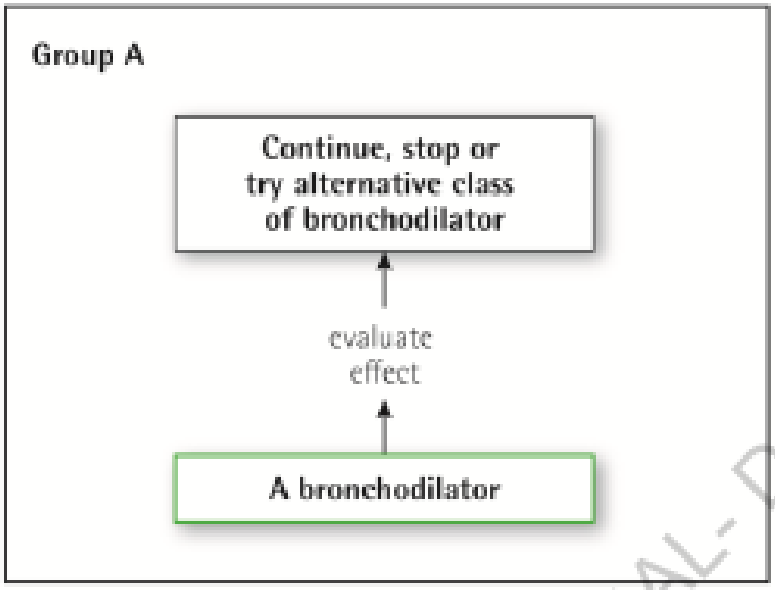


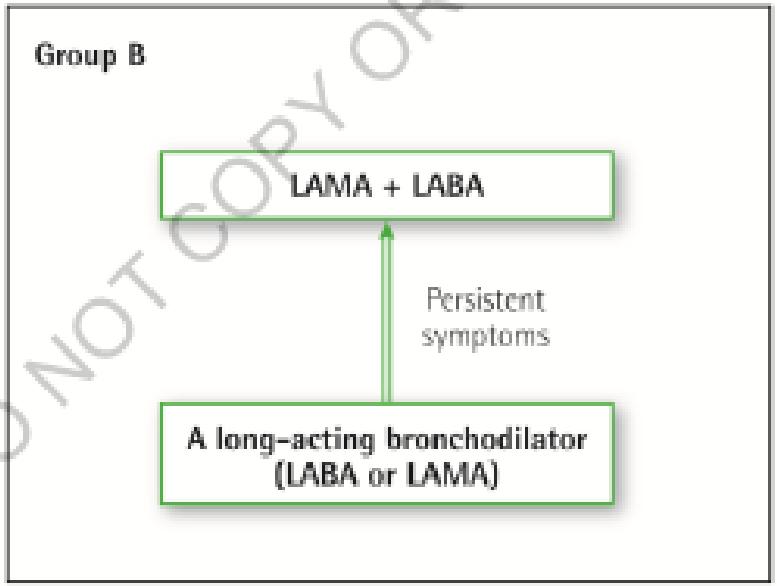
n, number of patients in the subgroup analysis
b.i.d., twice daily; IND/GLY, indacaterol/glycopyrronium 110/50 µg; o.d., once daily; SFC, salmeterol/fluticasone 50/500 µg

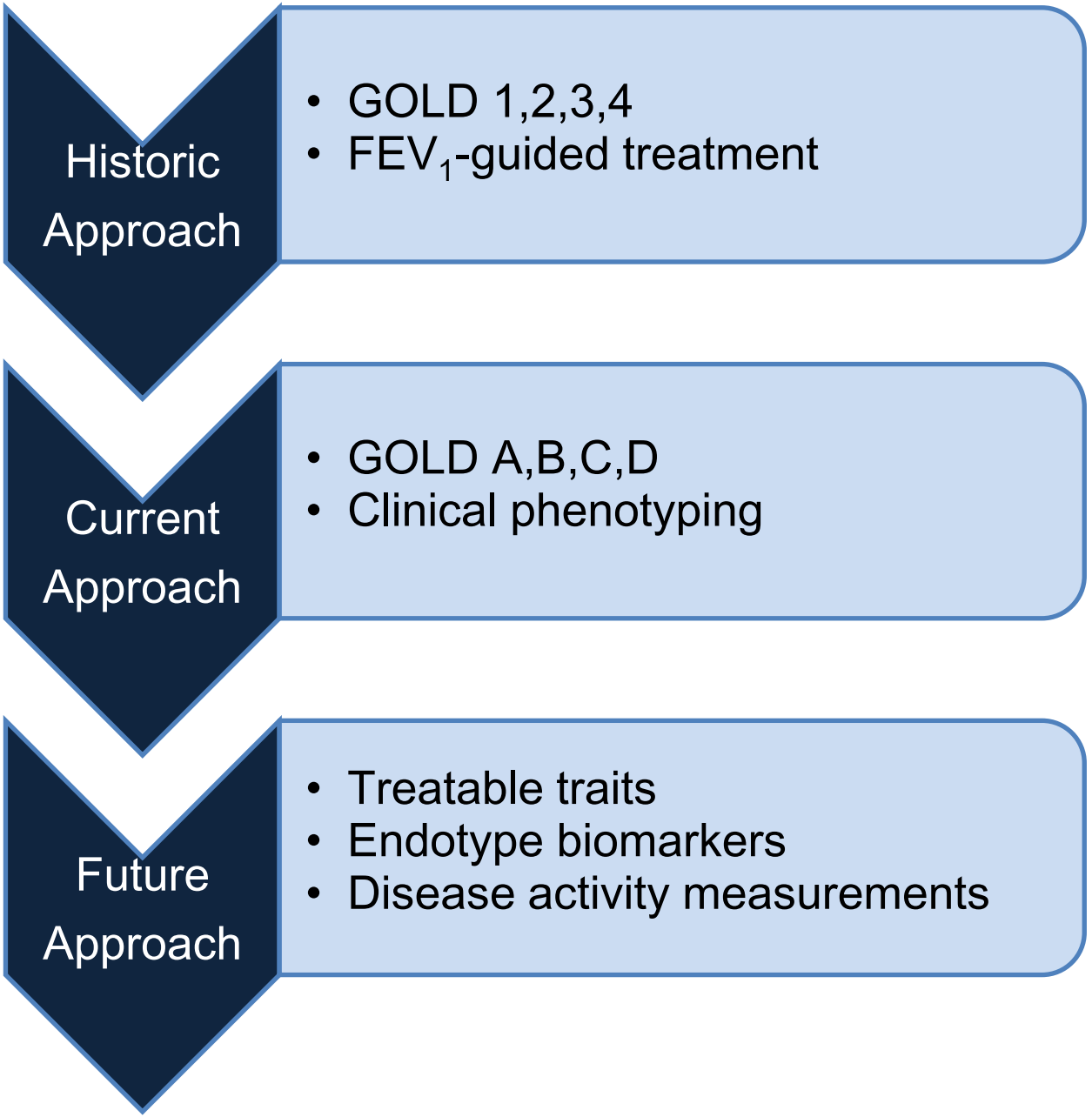
Kenneth et al. ERS poster 2016









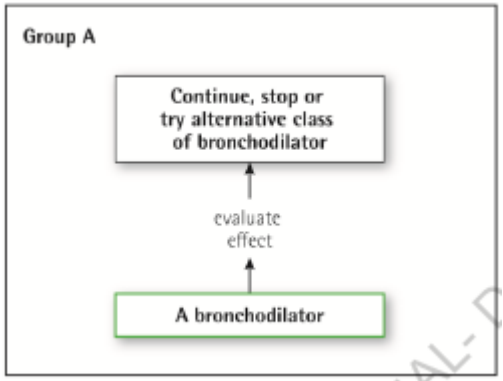


Singh et al. Am Jr Respi Cri Care Med 2016

경청해주셔서 감사합니다

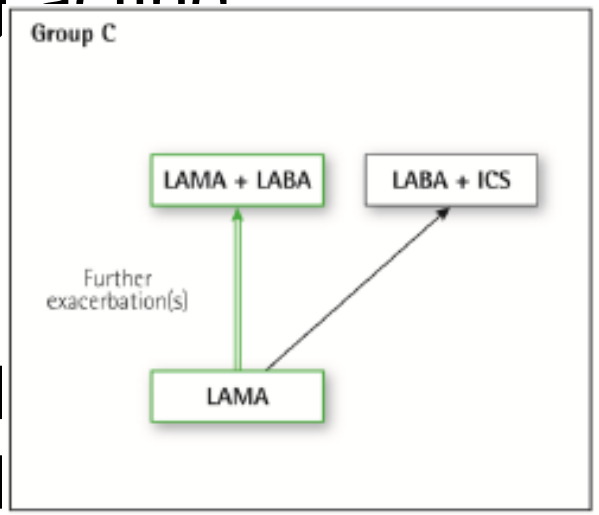
- Bronchodilator treatment based on its effect on breathlessness. Either short or long acting brondhocilator.

- Continued if symptomatic benfit is documented

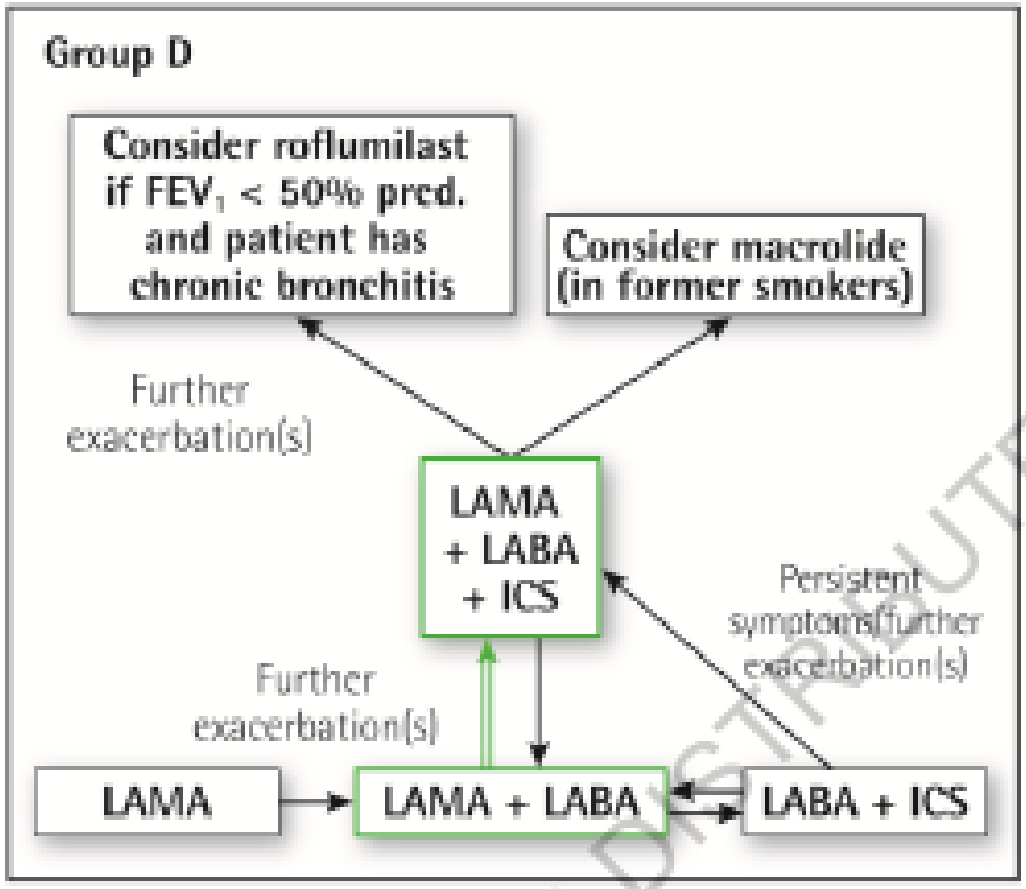


- Either LABA or LAMA. Choice should be depend on patient's perception of symptom relief.
- If persistnt breathlessness on monotherapy, two ronchodilators is recommended
- For patients with severe breathlessness, initial therapy with two bronchodilators maybe considered.
- If the addition of a second bronchodilator does not improve symptoms, treatment could be stepped down again to a single bronchodilator.

- Initial therapy with a single long acting bronchodilator.
- LAMA was superior to LABA re exacerbation prevention.
- Persistent exacerbations → add acting ronchodilator (LABA/LA ICS/LABA. Primary choice is LABA/LAMA because of risk for pneumonia in some patients



Stopping ICS, 폐렴 risk 높으면 가능



Bronchodilators in stable COPD

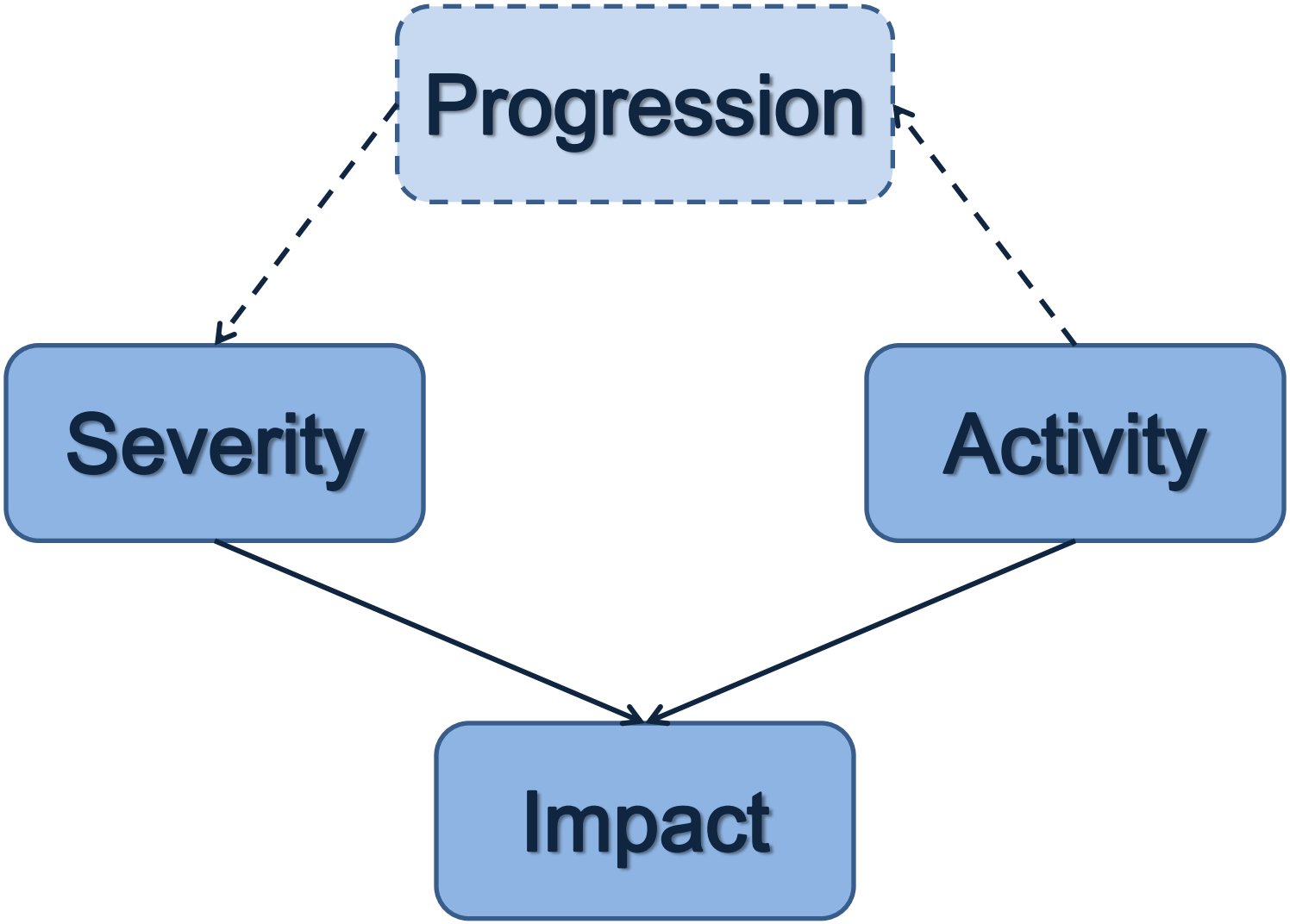
- LABAs and LAMA significantly improve lung function, dyspnea, health status, and reduce exacerbation rates.
- LAMA have greater effect on exacerbation reduction compared with LABAs and decrease hospitalizations.
- LABA+LAMA increases FEV1 and reduces symptoms compared to monotherapy
- LABA+LAMA reduces exacerbations compared to monotherapy or ICS/LABA
- Theophylline exerts small bronchodilator effect in stable COPD and that is associated with modest symptomatic benefits.

ICS in stable COPD

- ICS combined with LABA is more effective than individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD
- Triple therapy improves lung functions, symptoms and health status and reduces exacerbations compared to ICS/LABA or LAMA monotherapy.

- An ICS combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD **(Evidence A)**.
- Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease **(Evidence A)**.

GOLD 2017

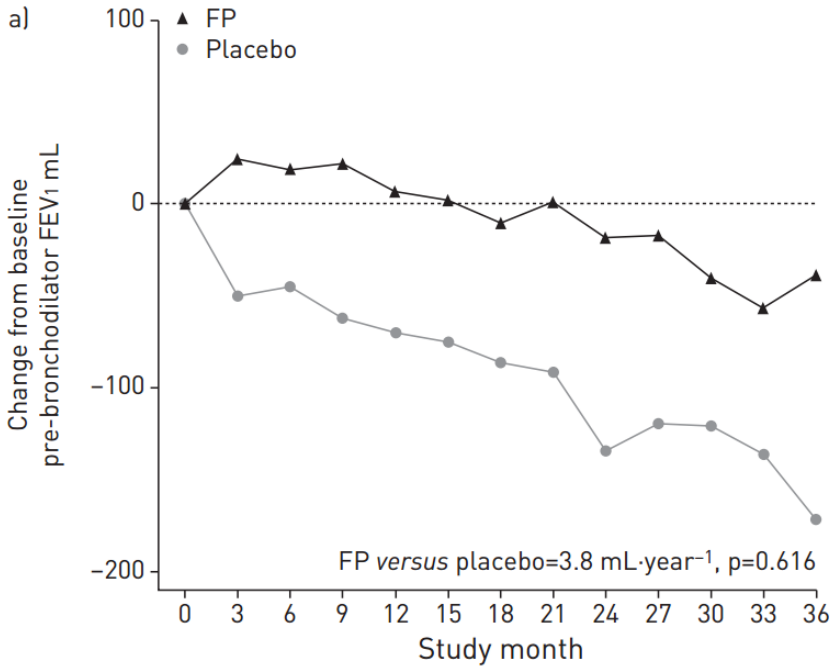


Singh et al. Am Jr Respi Cri Care Med 2016

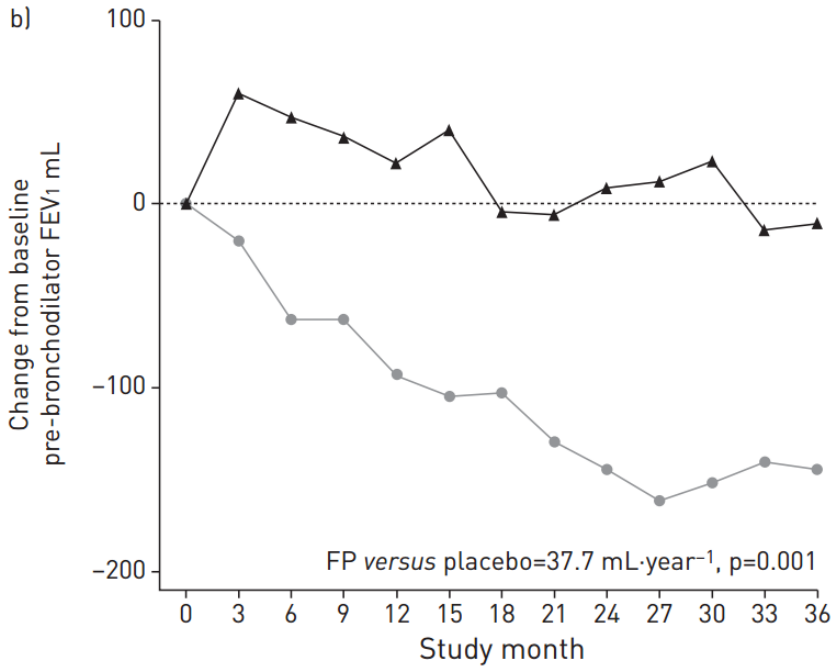
Blood eosinophils, marker for response to ICS

ISOLDE

blood eosinophil <2%



blood eosinophil ≥2%



Barnes et al. Eur Respir J 2016

RPL554 Has Bronchodilator and Anti - Inflammatory Properties

RPL554

X

X

PDE3
Airway Smooth muscle

Airway smooth muscle
(PDE3A,3B,4D)

Relaxation

Bronchodilation

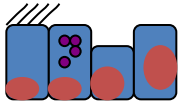
PDE4
Inflammatory cell types

Neutrophils
PDE4A,B,D

↓ MPO
↓ NE
↓ MMP-9
↓ Respiratory burst

Eosinophils
PDE4A,B,D

↓ LTC4

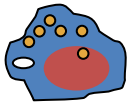


Epithelial cells
PDE3,4A,C,D

↓ TNF-a
↓ GM-CSF
↓ IL-6

Lymphocytes
PDE3,4A,B,D

↓ IL-4
↓ IL-5



Macrophages
PDE3,4A,B,D

↓ TNF-a
↓ superoxide

Anti-inflammatory effects

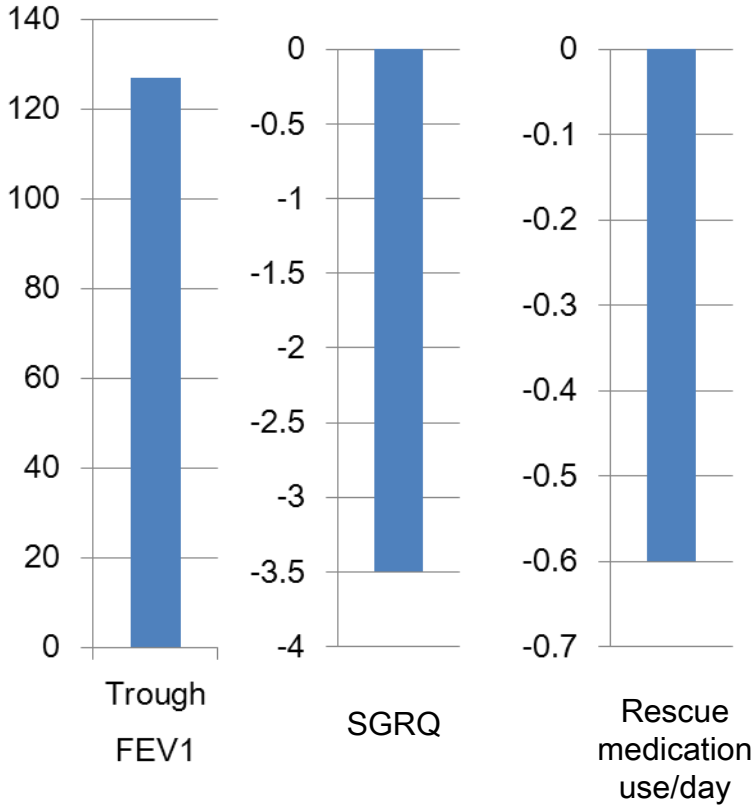
Slides from Dr. Clive Page

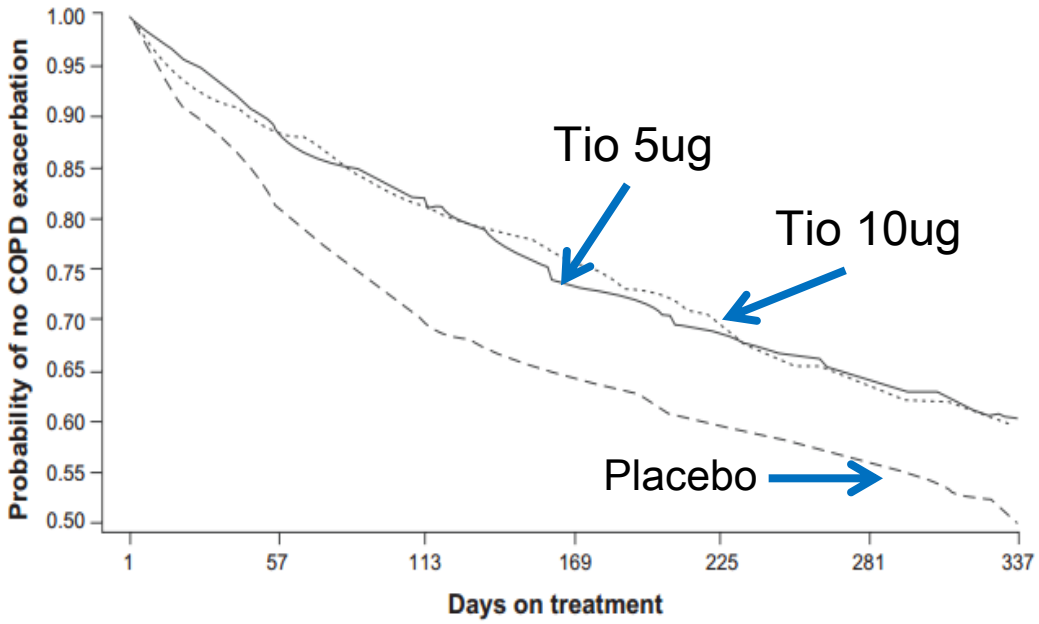
LAMA vs Placebo

Inclusion: $FEV_1 \leq 60\%$ pred, no COPD AE

- Tiotropium SMI 5ug (n=670)
- Tiotropium SMI 10ug (n=667)
- Placebo (n=653)

Duration: 1 yr





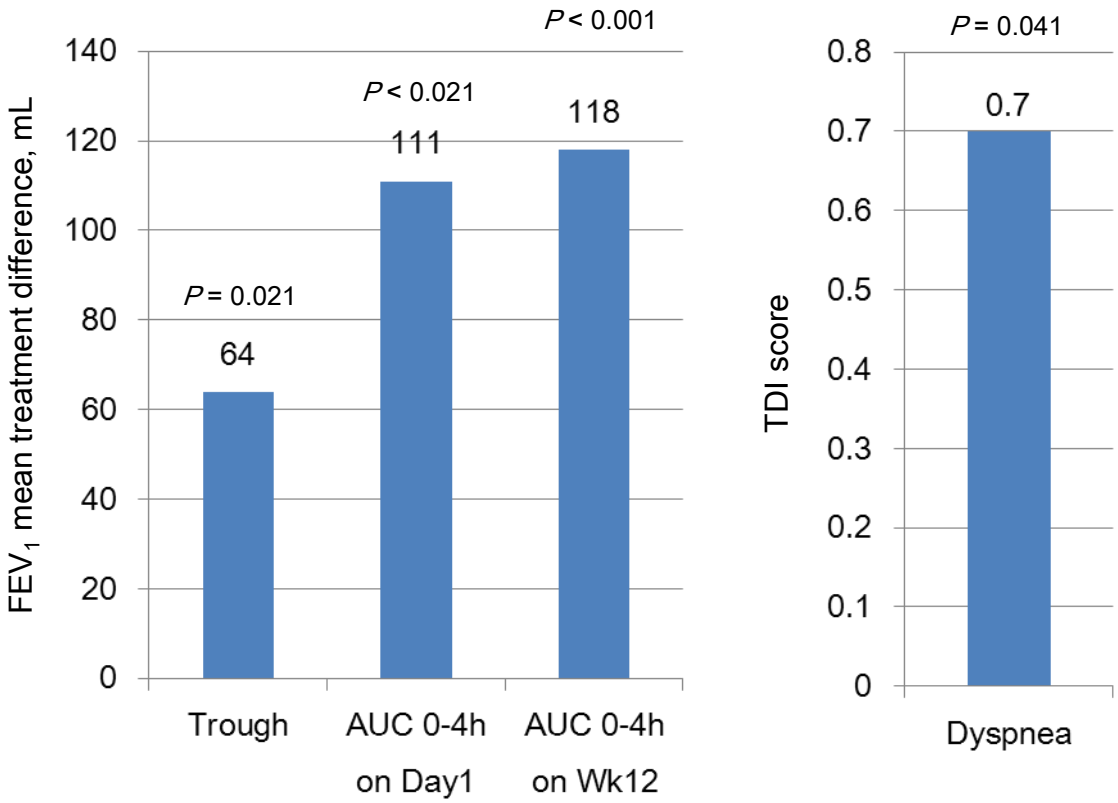
Bateman et al. Int Jr COPD 2010

GLOW6

Triple therapy vs ICS/LABA

Inclusion: 30% ≤ FEV_1 < 80% pred
- Glycopyrronium/indacaterol/corticosteroid 100/25 ug (n=138)
- Indacaterol/corticosteroid (n=142):

Duration: 12wks



Vincken et al. Int Jr COPD 2014
Vincken et al. Eur Respi Jr 2014