New Drugs in COPD

LABA/LAMA FDCs

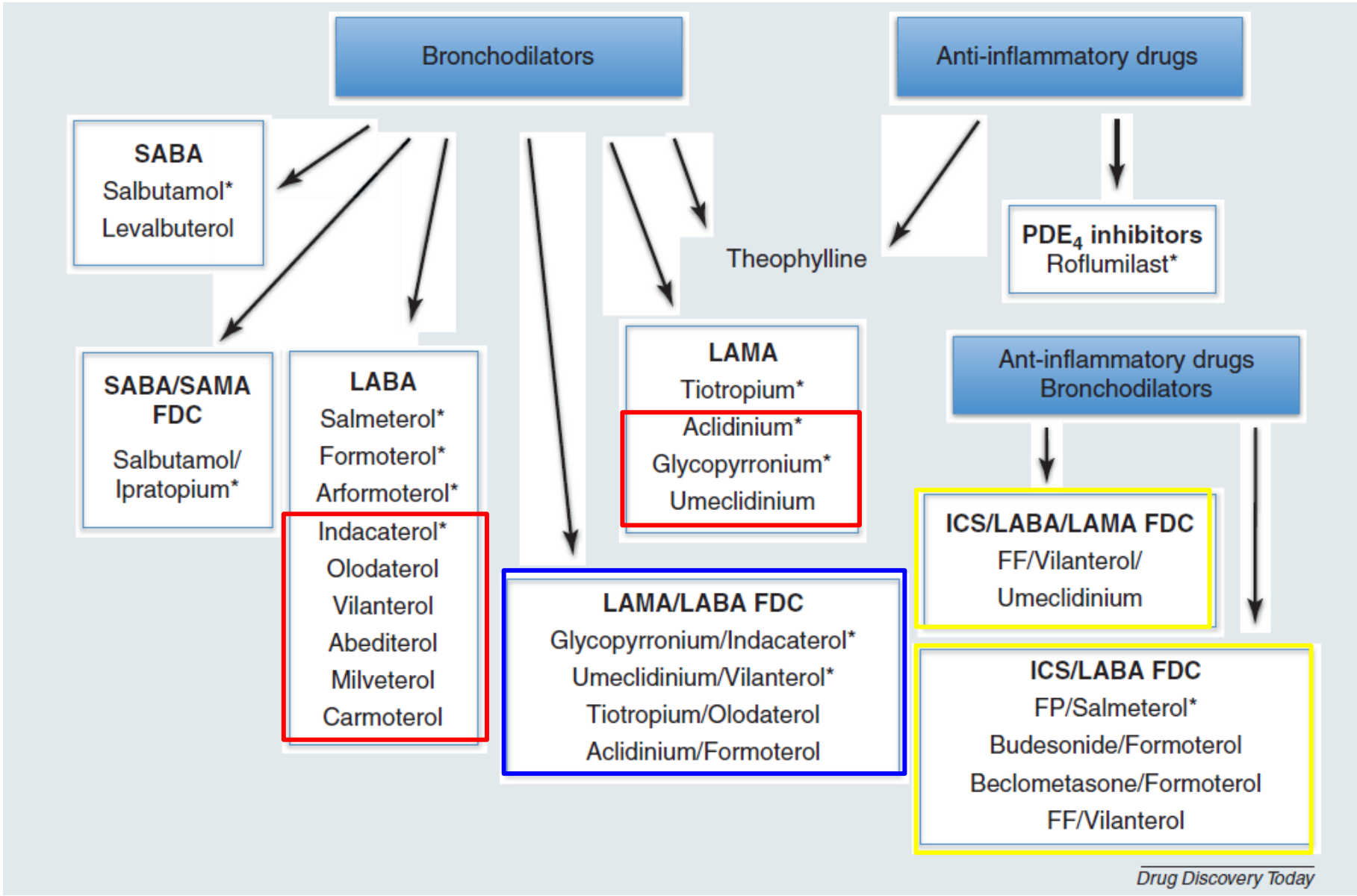
신경철

영남의대 호흡기·알레르기내과

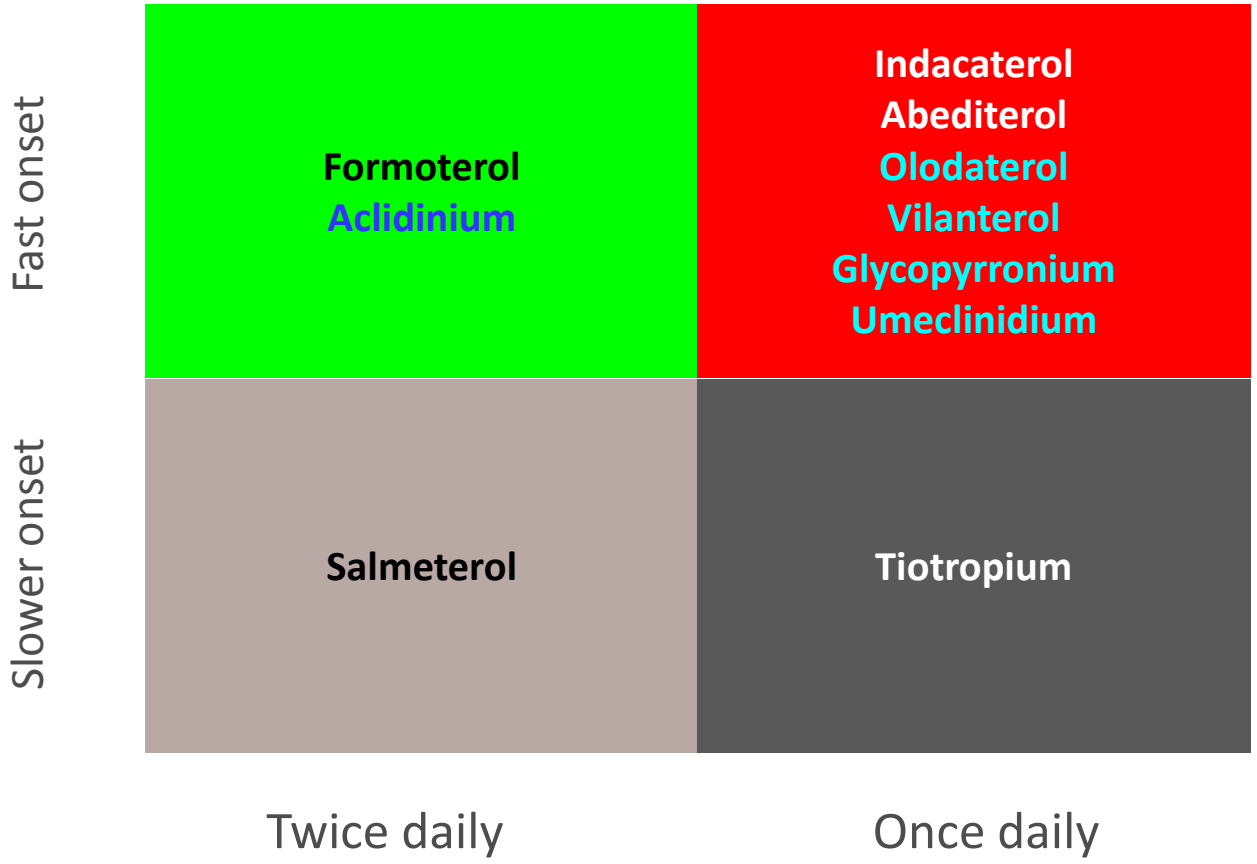
강의 순서

- New bronchodilators
- Efficacy of new bronchodilators: LABA and LAMA
- Benefits of LABA/LAMA FDCs
- Differences between LABA/LAMA FDCs
- Place of LABA/LAMA FDCs in COPD treatment

New bronchodilators in COPD

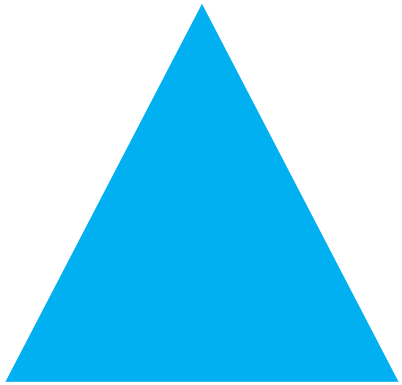


New bronchodilators in COPD



COPD 약물치료 시 평가사항

Degree of airflow limitation (FEV1)



Intensity of symptoms (Dyspnea)

Frequency of exacerbation

Others
- Rescue medication use
- Exercise performance
- Quality of life
- Disease progression
- Mortality

Bronchodilators: Key drug of stable COPD

Rationale for combination

LAMA + LABA

- Further benefits expected in
  - Lung function
  - Symptoms
  - Exercise tolerance
- Similar safety profile as individual therapies anticipated
- Increased convenience: patient only needs 1 inhaler

New combination bronchodilators

New combination	LAMA	LABA	Delivery device
Glycopyrronium+Indacaterol (Xoterna®)	Glycopyrronium	Indacaterol	Breezehaler
Umeclidinium+Vilanterol (Anoro®)	Umeclidinium	Vilanterol	Ellipta
Aclidinium+Formoterol (Duaklir®)	Aclidinium	Formoterol	Genuair
Tiotropium+Olodaterol (Vahelva®)	Tiotropium	Olodaterol	Respimat

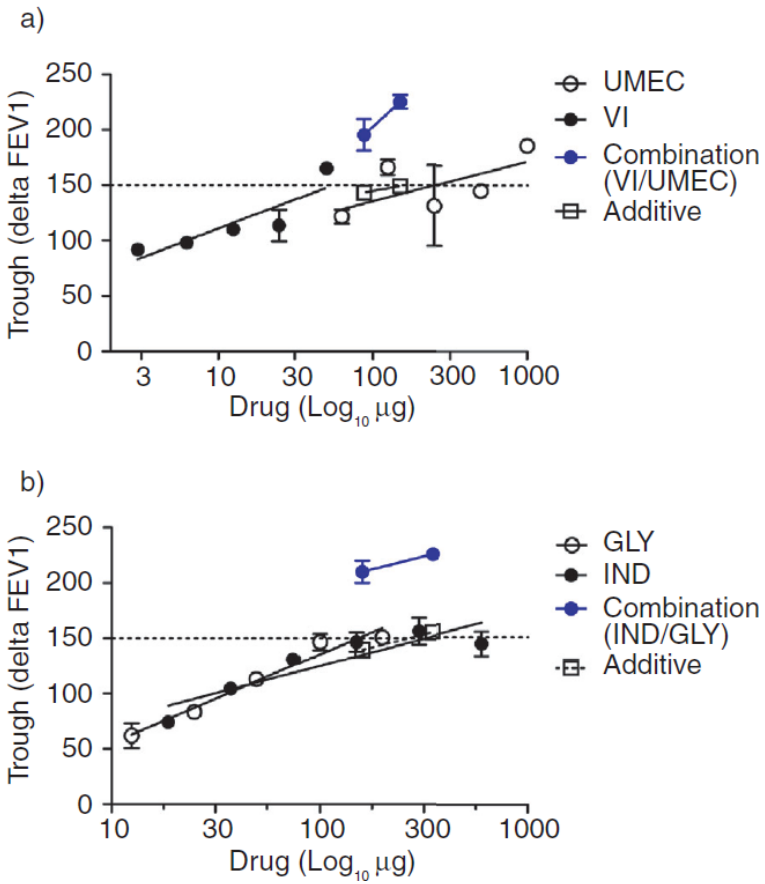
LABA/LAMA FDC: additive or synergistic?

- Synergistic is defined as the phenomenon whereby the pharmacological response to two drugs of different classes given in combination exceeds the response that could be explained by their additive effect.

- Various clinical trials have documented greater improvements in lung function but such improvements do not always translate to greater improvements in symptom scores or reduction in the rate of exacerbation compare with a single drug.

- Are LABA/LAMA FDCs synergistic?

LABA/LAMA FDC: synergistic?



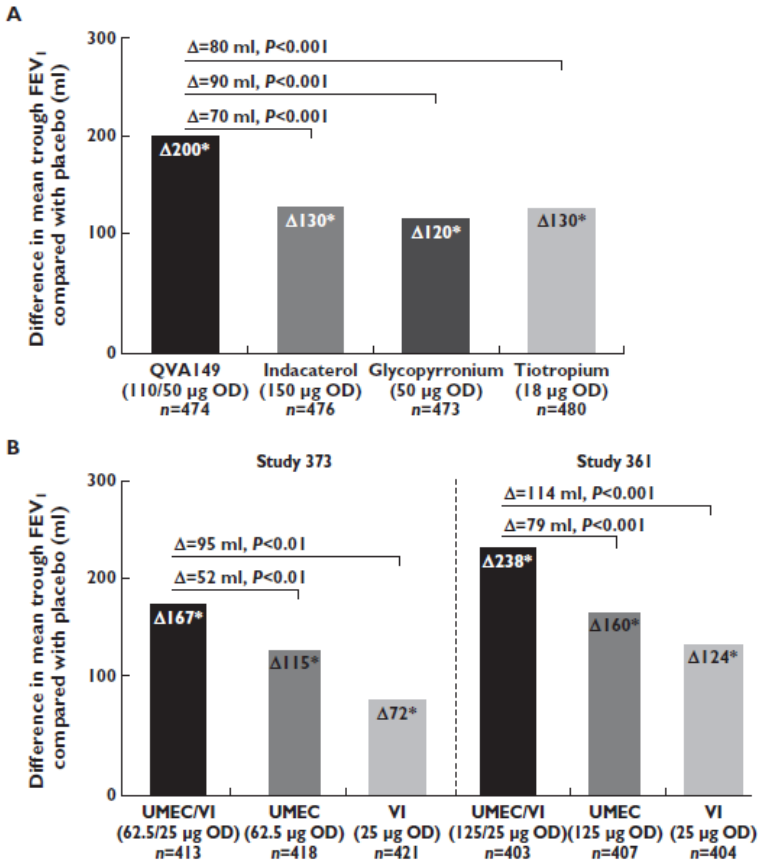
Dose response relationships for a LABA and a LAMA alone and in a fixed dose combination LABA/LAMA in patients with moderate to severe COPD. (a)Shows a linear regression for the dose response relationship for umeclidinium bromide (UMEC: open circles) and vilanterol (VI: closed circles) (b) glycopyrronium bromide (GLY: open circles) and indacaterol (IND: closed circles). The theoretical additive response (open squares) and the observed response (circles; blue) for fixed dose combinations of these bronchodilators are superimposed. The combination effect was shown to be synergistic (see Table 2).

Eur Clin Res J 2015:2;1-15

Lung function: trough FEV_1

GLY/IND

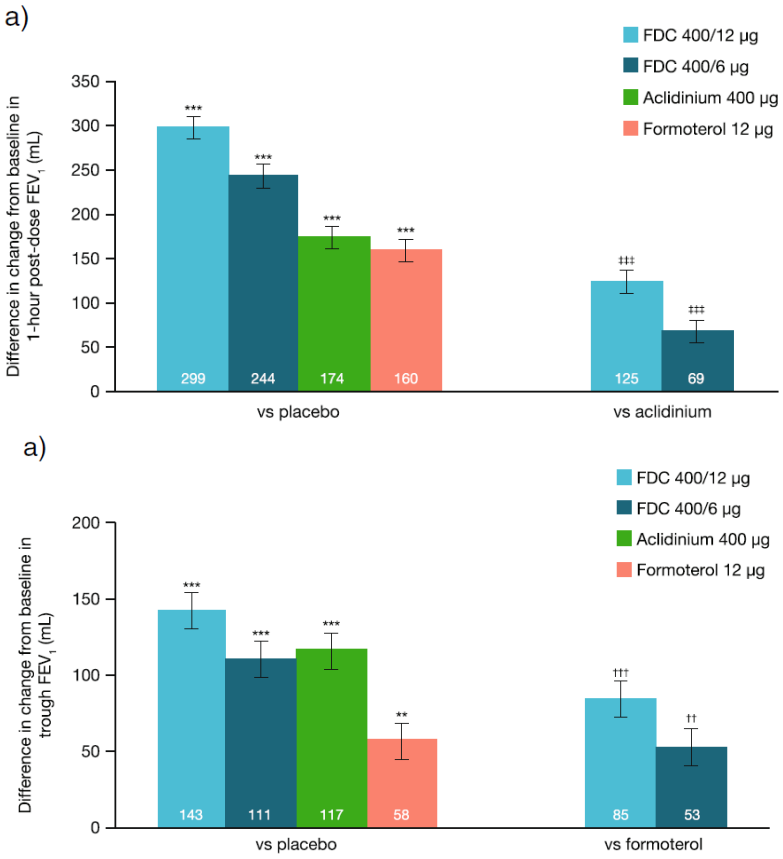
UMEC/VIL



Effect of QVA149, its monocomponents and tiotropium (A) and UMEC/VI and its monocomponents (B) on mean trough FEV1 at week 26. (A) SHINE trial data; (B) studies 373 and 361 data.*$P < 0.001$ for comparisons with placebo. The horizontal lines are the comparisons of QVA149 with indacaterol, glycopyrronium (primary end point) and tiotropium in (A) and of UMEC/VI with UMEC and VI alone (primary end point) in (B)

Br J Clin Pharmacol 2014:79;695-708

Lung function: Post-dose FEV_1 & trough FEV_1 (Aclidinium/formoterol)

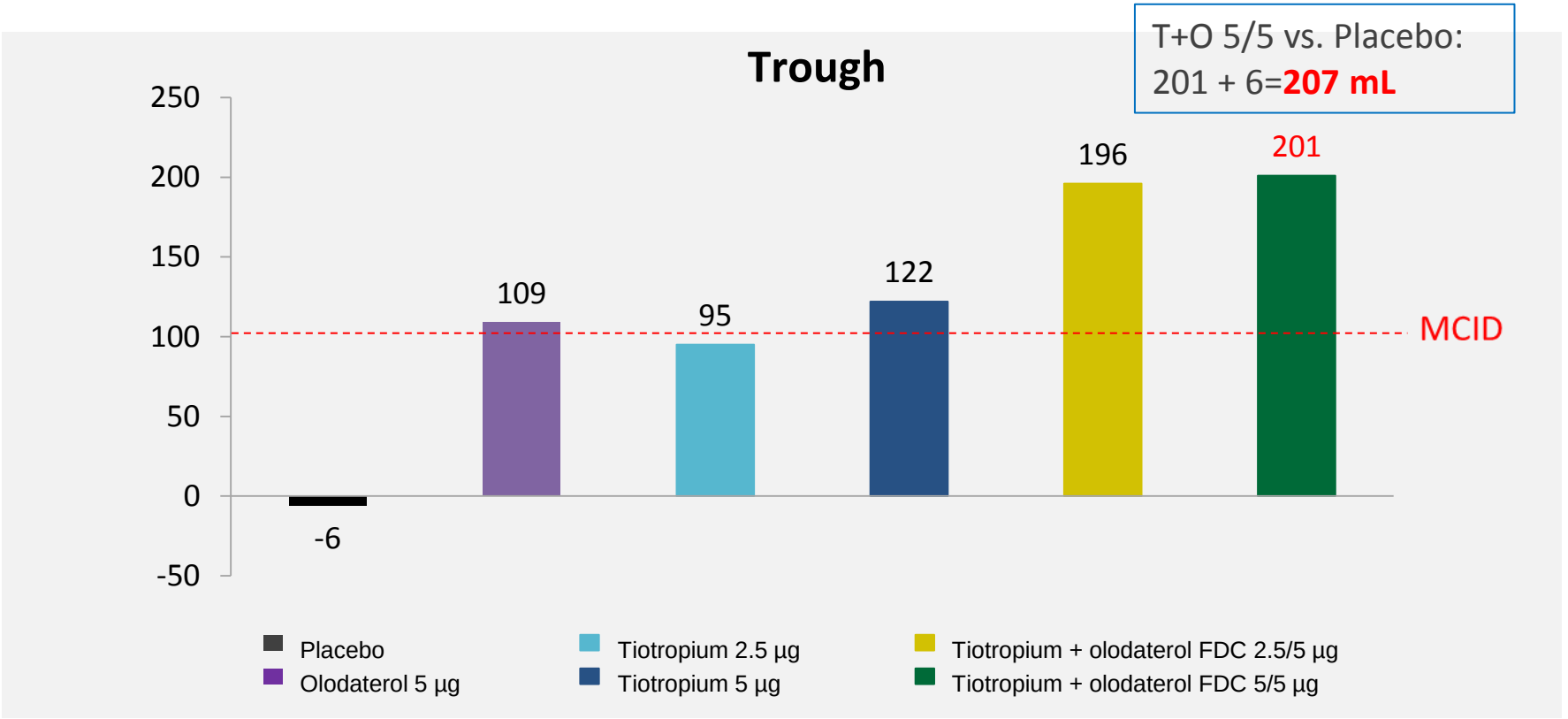


- Aclidinium/formoterol vs aclidinium (1 hour post-dose FEV1)
  - 400/12 µg 125 mL ($p < 0.001$)
  - 400/6 µg 69 mL ($p < 0.001$)
- Aclidinium/formoterol vs formoterol (Trough FEV1)
  - 400/12 µg 85 mL ($p < 0.001$)
  - 400/6 µg 53 mL ($p < 0.01$)

BMC Pulmonary Medicine 2014, 14:178

Lung function: trough FEV_1 (Tiotropium/Olodaterol)

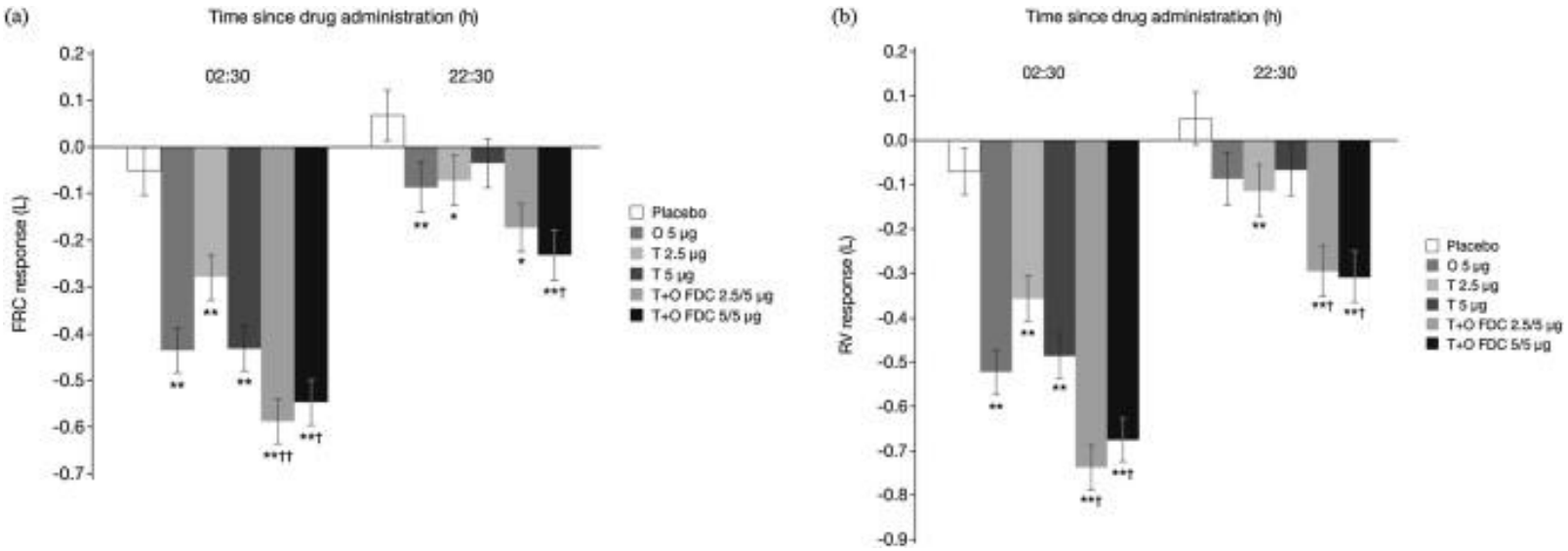
Adjusted trough FEV_1 responses after 6 weeks of treatment



FDC, fixed-dose combination; FEV_1, forced expiratory volume in 1 second.

Beeh KM, et al. Pulm Pharmacol Ther 2015; May 6. pii: S1094-5539(15)00044-9. doi: 10.1016/j.pupt.2015.04.002.

Lung function: FRC & RV
(Tiotropium/Olodaterol)



Air trapping 개선

Fig. 4. Adjusted mean FRC (a) and RV (b) responses at 6 weeks ± SE, measured by body plethysmography at 2 h 30 min and 22 h 30 min post-dose. *p < 0.05 versus placebo; **p < 0.0001 versus placebo; †p < 0.05 versus all monotherapies; ††p < 0.01 vers...

Kai-Michael Beeh, Jan Westerman, Anne-Marie Kirsten, Jacques Hébert, Lars Grönke, Alan Hamilton, Kay Tetzlaff, Eric Derom **The 24-h lung-function profile of once-daily tiotropium and olodaterol fixed-dose combination in chronic obstructive pulmonary disease**

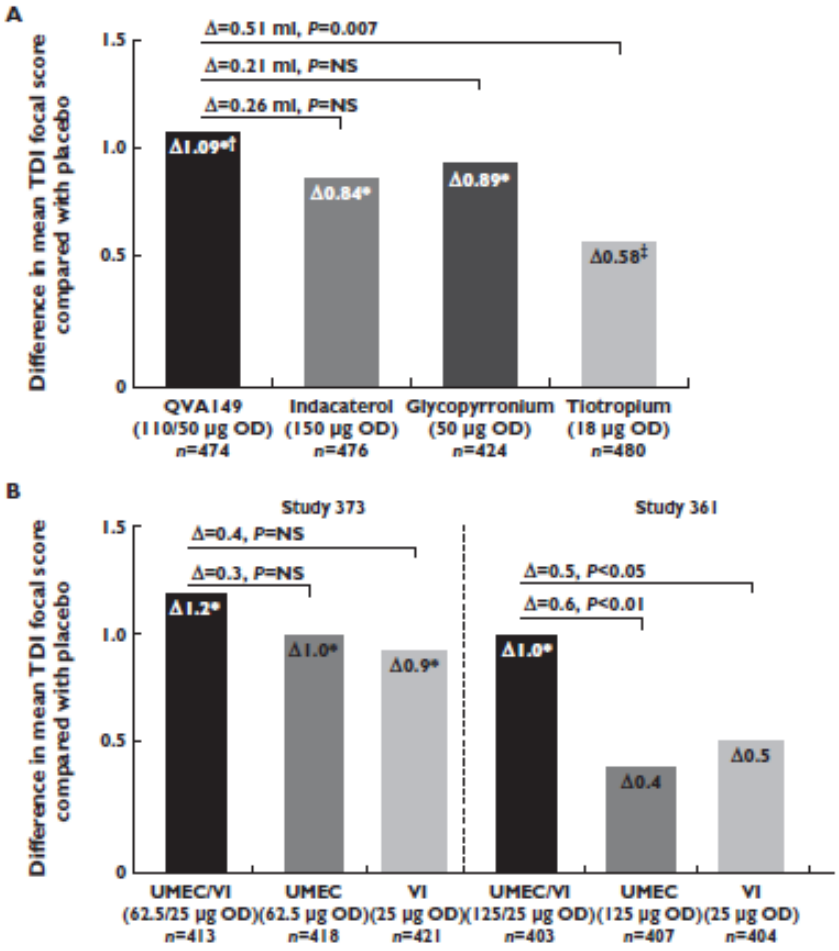
Pulmonary Pharmacology & Therapeutics, Volume 32, 2015, 53–59

http://dx.doi.org/10.1016/j.pupt.2015.04.002

Symptoms: Dyspnea (TDI)

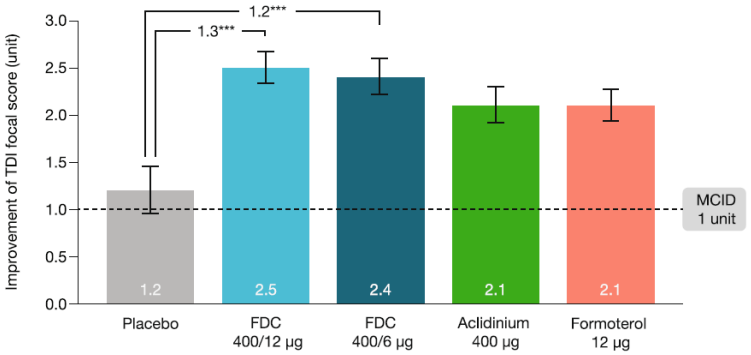
GLY/IND

UMEC/VIL



Br J Clin Pharmacol 2014:79;695-708

Symptoms: Dyspnea (TDI)

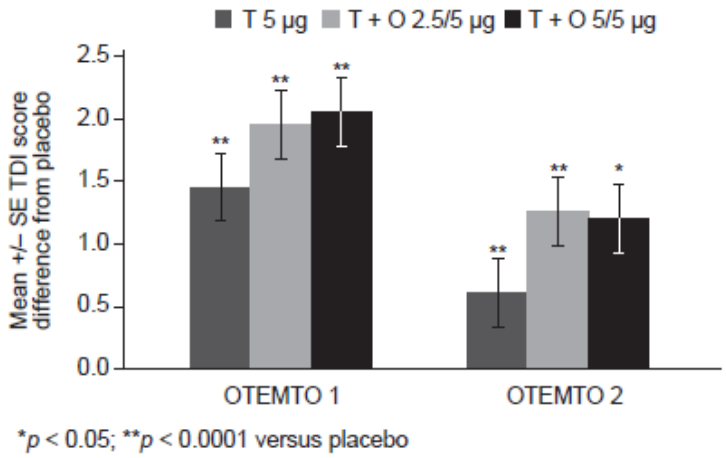


Improvement in **TDI** focal score at 24 weeks (ITT population)
***p < 0.001 vs placebo.

Aclidinium/formoterol

- FDC vs placebo: 1.29unit/1.16 unit (p<0.001)
- FDC vs monotherapy: not significant

BMC Pulmonary Medicine 2014, 14:178



*p < 0.05; **p < 0.0001 versus placebo

Tiotropium/olodaterol

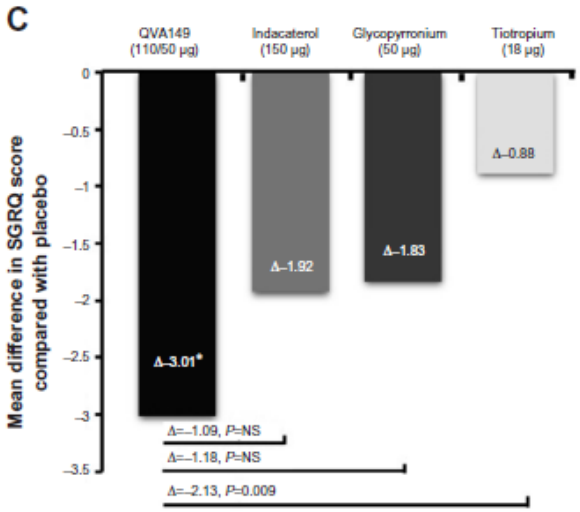
- Tiotropium + olodaterol 5/5 mg increased TDI focal score by 2.05 (OTEMTO 1) and 1.20 (OTEMTO 2) units compared to placebo

Mean difference from placebo in TDI score after 12 weeks (full analysis set).

Respiratory Medicine 109 (2015) 1312e1319

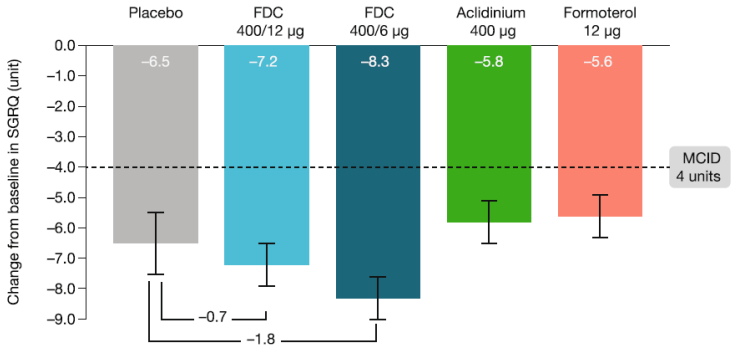
Symptoms: SGRQ

Glycopyrronium + Indacaterol



Br J Clin Pharmacol 2014:79;695-708

Aclidinium + Formoterol



SGRQ: high placebo effect

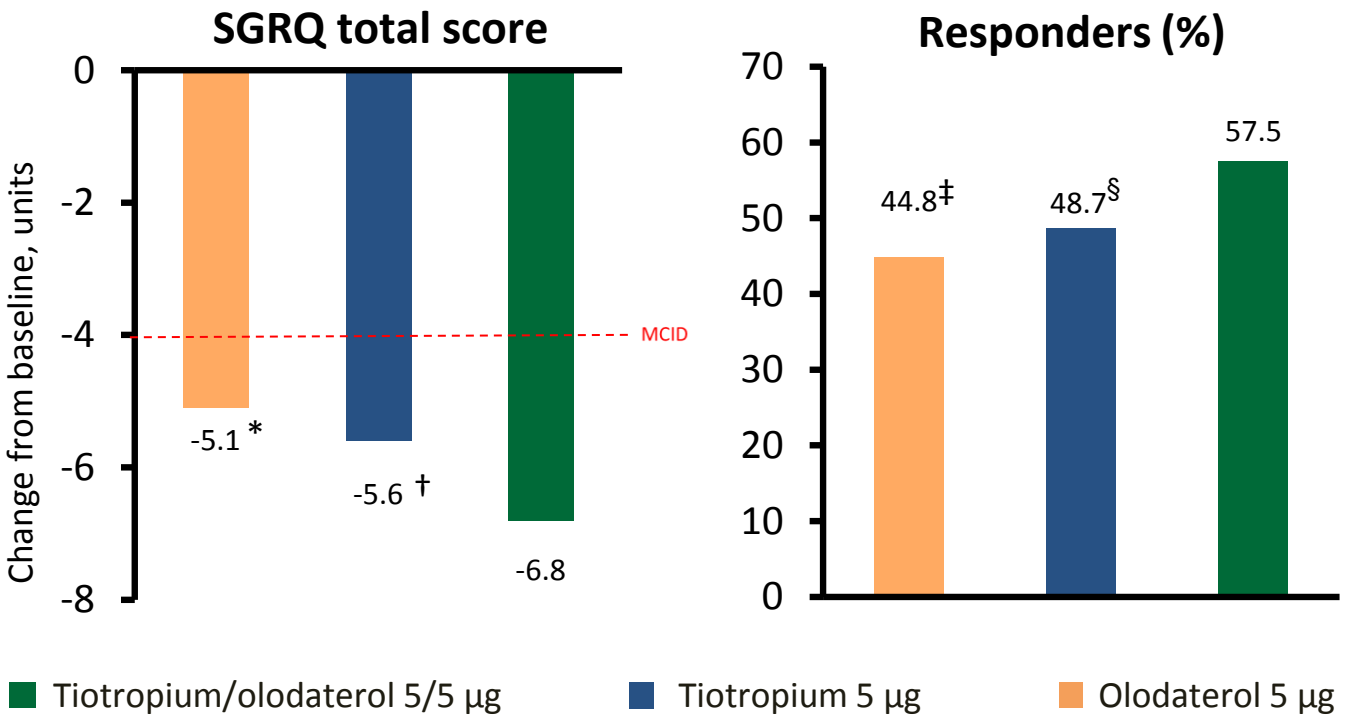
- FDC vs placebo: not significant
- FDC vs monotherapy: not significant

Change from baseline in **SGRQ** total score at 24 weeks (ITT population).

BMC Pulmonary Medicine 2014, 14:178

Symptoms: SGRQ (Tiotropium/Olodaterol)

Tiotropium/Olodaterol



*p=0.0022 vs tiotropium/olodaterol 5/5 µg; †p=0.252 vs tiotropium/olodaterol 5/5 µg;
‡p<0.0001 vs tiotropium/olodaterol 5/5 µg; § p=0.001 vs tiotropium/olodaterol 5/5 µg.

Buhl RM, et al. Eur Respir J 2015; 45: 969–979.

Rescue medication:
(Glycopyrronium/Indacaterol vs Tiotropium)

TABLE 2] Effect of QVA149 vs Tiotropium on Secondary COPD Outcomes

Outcome	Studies	Patients, No.	Estimate	Effect (95% CI)	I^2, % (*P* Value)
Change in total TDI score from baseline to end of treatment, mean	11,21	1,397	MD	−0.57 (−0.88, −0.27)	0 (.0002)
Patients with a minimally clinically important difference in TDI at week 26 (≥1 points), %	11,21	1,307	RR	1.19 (1.03, 1.37)	22 (.01)
			NNTB	11 (7, 26)	
Change from baseline in health status (SGRQ) at the end of treatment, mean	11,20	2,315	MD	−2.64 (−5.15, −0.14)	0 (.04)
Patients with minimally clinically important difference in SGRQ at end of treatment (≥4 points), %	11,20	1,384	RR	1.16 (1.09, 1.25)	0 (.0001)
			NNTB	11 (8, 20)	
Rescue medication use, puffs/d	11,20	2,080	MD	−0.63 (−0.77, −0.48)	80 (.0001)
Patients with COPD exacerbations	11,20	1,400	RR	0.91 (0.84, 0.99)	26 (.03)
			NNTB	19 (11, 73)	
Any AE	11,20,22	3,181	RR	1.01 (0.95, 1.06)	15 (.83)
Total withdrawals	11,20,22	3,191	RR	1.00 (0.74, 1.37)	31 (.98)
Withdrawals due to AEs	11,20,22	2,578	RR	1.13 (0.53, 2.41)	40 (.75)

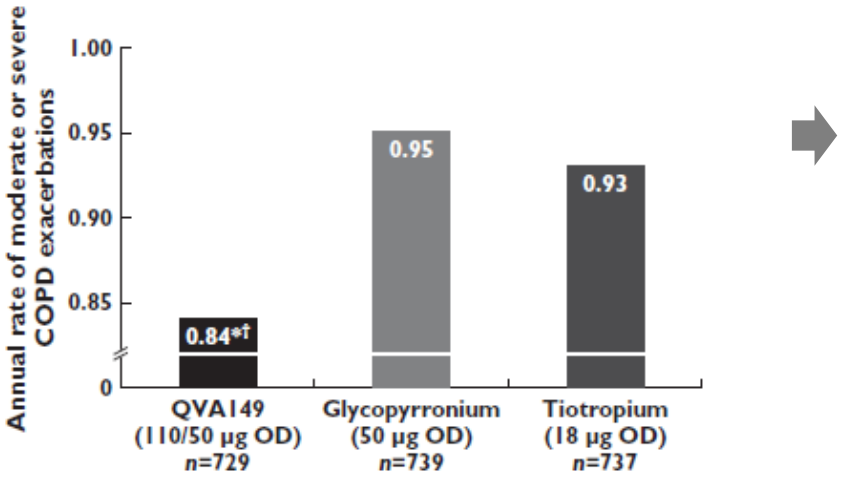
MD = mean difference; NNTB = number needed to treat for benefit; RR = relative risk; SGRQ = St. George's Respiratory Questionnaire; TDI = Transitional Dyspnea Index. See Table 1 legend for expansion of other abbreviations.

CHEST 2014; 146(2):309- 317

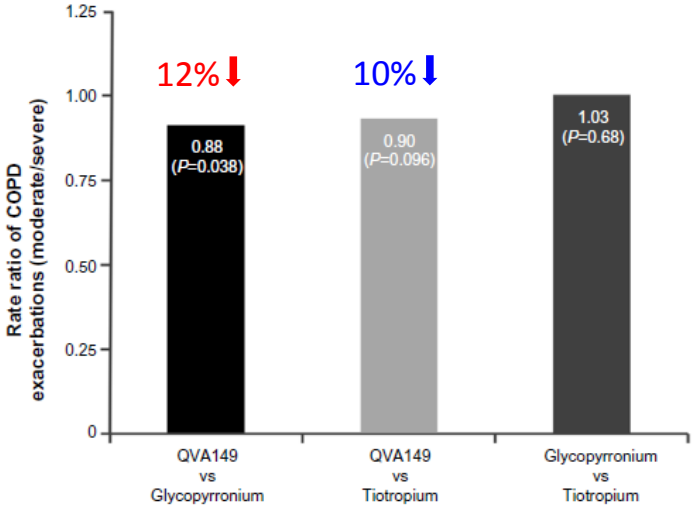
LABA/LAMA FDCs in COPDs with a history of exacerbation

Glycopyrronium/indacaterol versus tiotropium (SPARK study)

- 2,224 patients
- COPD GOLD III-IV (FEV_1 <50%)
- One and more exacerbation in the past year



Annual rate of moderate or severe COPD exacerbations according to treatment group (SPARK trial). *P = 0.038 for comparison with glycopyrronium. †P = 0.096 for comparison with tiotropium. OD once Daily (Br J Clin Pharmacol 2014:79;695-708)



Moderate to severe exacerbation
(International Journal of COPD 2015:10 111–123)

*SPARK trial: Lancet Respir Med. 2013;1(3):199–209.

LABA/LAMA FDCs in COPDs without a history of exacerbation

- LABA/LAMA or ICS/LABA?
  - Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol–fluticasone: GOLD stages II–III, without exacerbations in the previous year[ILLUMINATE]

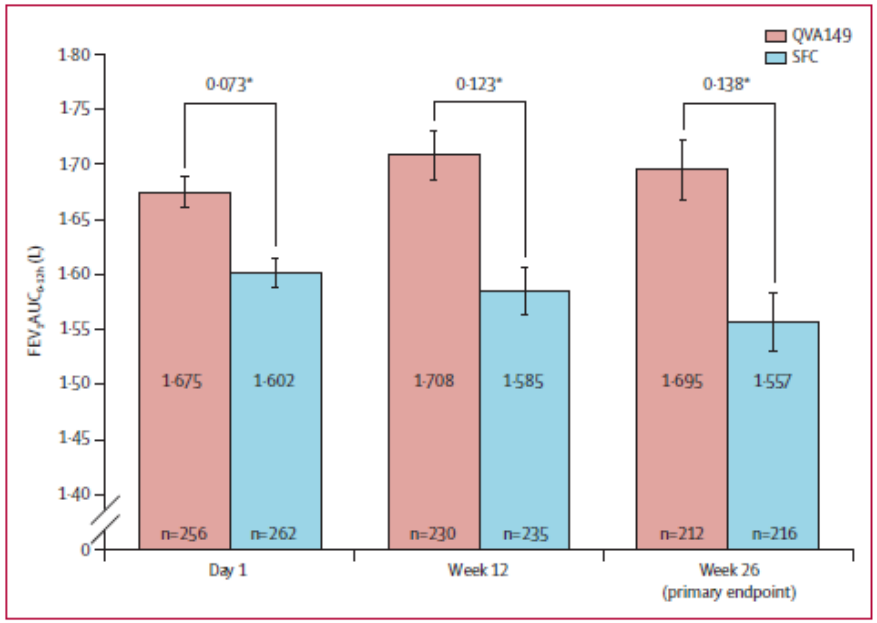


Figure 3: **FEV$_1$ AUC$_{0-12h}$**
Data are least squares mean (SE). Numbers shown represent patient number per treatment group at each timepoint. FEV$_1$=forced expiratory volume in 1 second. AUC$_{0-12h}$=area under the plasma concentration-time curve from 0 to 12 h. SFC=salmeterol–fluticasone. *p<0·0001 for comparisons between QVA149 and SFC.

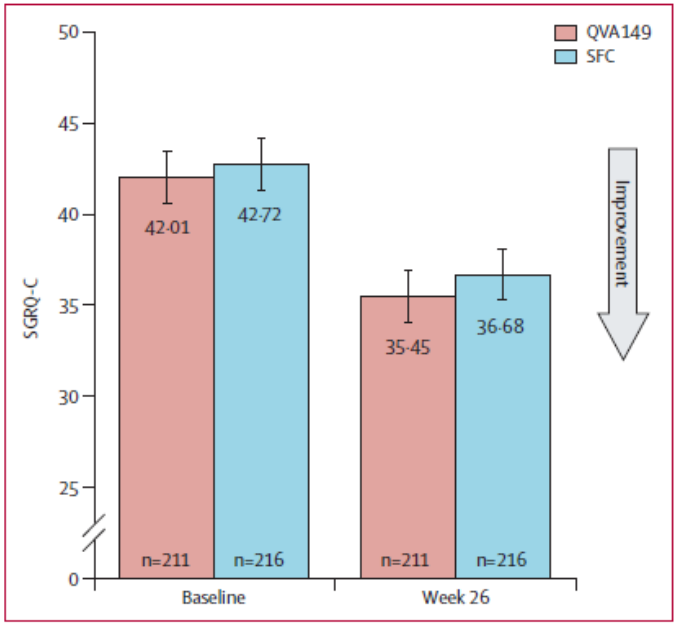


Figure 6: **Mean SGRQ-C total score**
Data are LSM (SE). Mean difference in SGRQ-C total score for QVA149 versus SFC at week 26 was −1·24 (p=0·25). SGRQ=St George's Respiratory Questionnaire. LSM=least squares mean. SE=standard error. SFC=salmeterol–fluticasone.

*ILLUMINATE trial: Lancet Respir Med. 2013;1:51-60

Comparison of LABA/LAMA FDCs with ICS/LABA FDCs

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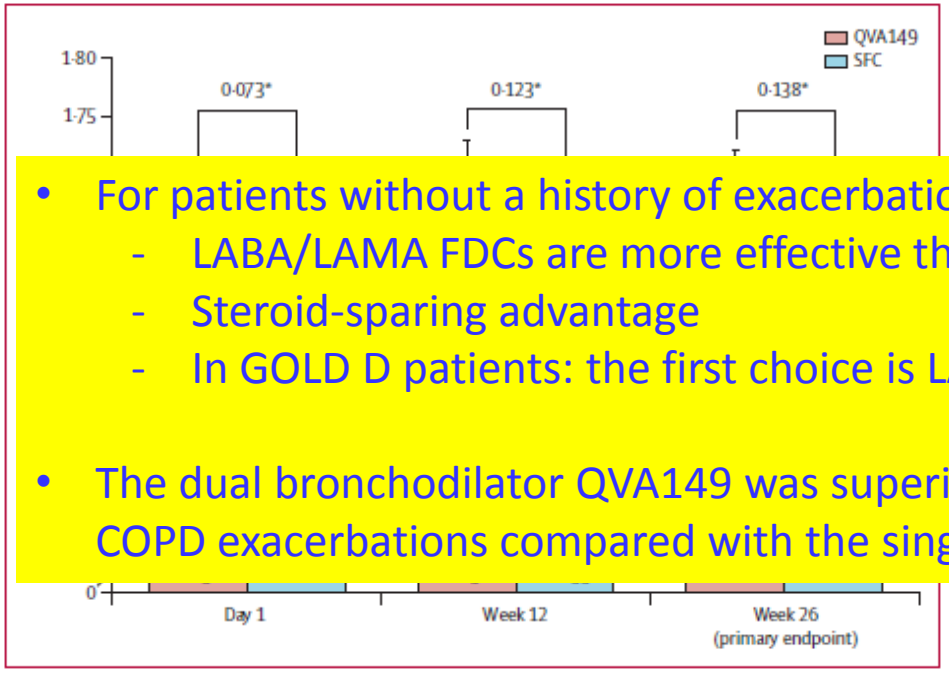

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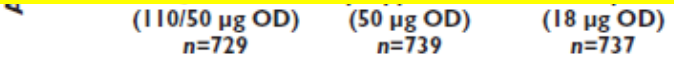
GLY/IND versus tiotropium (SPARK study): 2,224 patients

- COPD GOLD III-IV (FEV$_1$ <50%)
- One and more exacerbation in the past year

- For patients without a history of exacerbation,
  - LABA/LAMA FDCs are more effective than ICS/LABA
  - Steroid-sparing advantage
  - In GOLD D patients: the first choice is LABA/LAMA FDC
- The dual bronchodilator QVA149 was superior in preventing moderate to severe COPD exacerbations compared with the single LAMA (glycopyrronium)



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Comparison of LABA/LAMA FDCs with ICS/LABA FDCs

GlY/IND vs ICS/LABA: LANTERN study

- 744 patients with moderate-to-severe COPD with a history of 1≤ exacerbations in the previous year, mMRC≥2
- QVA149 110/50 µg once daily or SFC 50/500 µg twice daily for 26 weeks.
- The primary endpoint was non-inferiority of QVA149 versus SFC for trough FEV_1 at week 26.

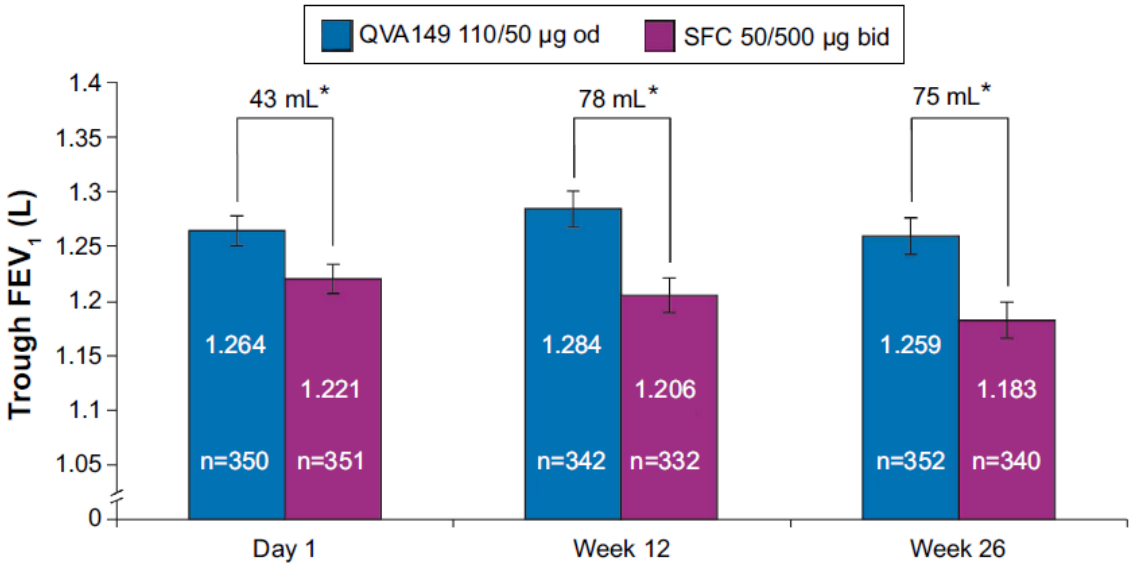

Figure 3 Trough FEV1 on day 1 and at weeks 12 and 26 (full analysis set). **Notes:** Data are least square means ± standard error; *P<0.001. **Abbreviations:** bid, twice daily; FEV1, forced expiratory volume in 1 second; od, once daily; SFC, salmeterol/fluticasone.

LANTERN: a randomized study of QVA149 versus salmeterol/fluticasone combination in patients with COPD. International Journal of COPD 2015:10 1015–1026

Comparison of LABA/LAMA FDCs with ICS/LABA FDCs

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- The primary endpoint was non-inferiority of QVA149 versus SFC for trough FEV_1 at week 26.

- LABA/LAMA, QVA149 as an alternative treatment, over LABA/ICS, in the management of moderate-to-severe COPD patients (GOLD B and GOLD D) with a history of ≤1 exacerbation in the previous year.
- LABA/LAMA FDC would not be inferior to ICS/LABA FDC for patients with a history of exacerbation(?)

Probability of exacerbation (%)

Days

Patients with exacerbation (%)				
QVA149: 0 (0.0%)	12 (3.3%)	20 (5.5%)	31 (8.6%)	43 (12.1%)
SFC: 0 (0.0%)	24 (6.6%)	38 (10.5%)	48 (13.4%)	67 (18.9%)

Figure 5 Kaplan–Meier plots of the time to first moderate or severe COPD exacerbation over 26 weeks of treatment (full analysis set).

≥4	0	0
Total number of exacerbations	53	81
Total number of treatment years	179.2	174.9
Rate of exacerbations per year	0.30	0.46
Treatment comparison versus SFC		
Ratio of rate (95% CI)	0.69 (0.48, 1.00)*	31% ↓

Note: *P<0.05.
Abbreviations: SFC, salmeterol/fluticasone; CI, confidence interval, od, once daily; bid, twice daily.

Table 3 Summary and analysis of COPD exacerbations over 26 weeks by treatment group (full analysis set)

LANTERN: a randomized study of QVA149 versus salmeterol/fluticasone combination in patients with COPD. International Journal of COPD 2015:10 1015–1026

Differences between LABA/LAMA FDCs

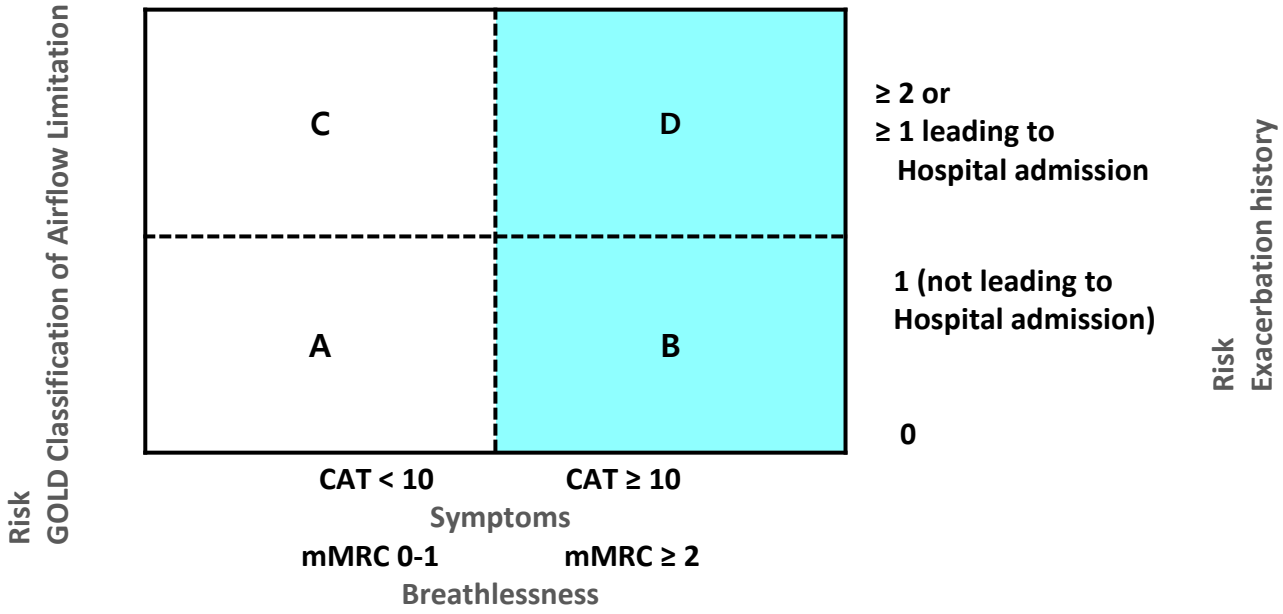
- Insufficient clinical data
- No head to head study

- GLY/IND, Umec/VI and Tio/Olo
  - Broadly similar in lung function
  - Once per day

- Aclidinium/formoterol
  - Twice per day, less convenient
  - Better suited to patients with night time or early morning symptoms

Place of LABA/LAMA FDCs in COPD treatment

- Clinical study design for LABA/LAMA FDCs
  - Moderate to severe COPD patients
  - mMRC2 or more / without acute exacerbation

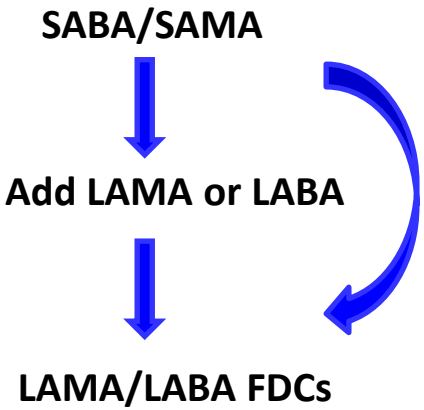


- GOLD B & D: LABA/LAMA FDCs are superior to monotherapy

Place of LABA/LAMA FDCs in COPD treatment

- **GOLD D: LABA/LAMA or ICS/LABA?**
  - With disease progression, patients who suffer with exacerbation
  - **'Triple therapy'**

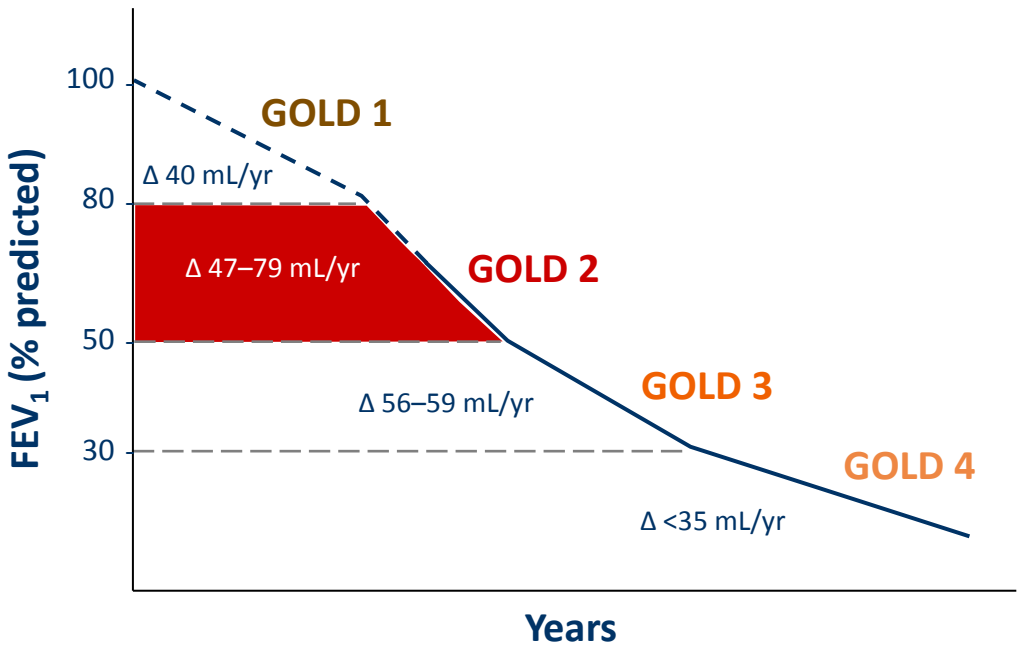
- **Optimal treatment sequence in patients without exacerbation**



For patients with more symptomatic or lower FEV1 consider LABA/LAMA FDC without trying monotherapy

Place of LABA/LAMA FDCs in COPD treatment Target?

by Tantucci : Patients with GOLD 2 have the steepest decline in FEV_1



Tantucci C, Modina D. Int J Chron Obstruct Pulmon Dis 2012; 7: 95–99; Welte T, et al. Int J Clin Pract; 2014; 69:336–349.

New treatment =Better outcome?

- We know more about COPD.
- Beginning to know: Who and when to give the drug.
- Yes, new treatment = better outcome but we need more.

New treatment
Better outcome

Morbidity ↓
Mortality ↓

- Diagnose early COPD
- Spirometry facility
- Increase awareness
- How to recognize
- How to treat
- Why & how to use inhalers

Conclusion

- LABA/LAMA FDCs offer a simplified means of maximizing bronchodilation for COPD patients
- LABA/LAMA FDCs have show greater effects on lung function than monocomponent.
- LABA/LAMA FDCs differ in terms of frequency of administration and inhaler device, which are likely to be key factors in determining their use in clinical practice.
- The relative clinical efficacy and safety of these drugs can only be properly determined by head-to-head clinical trials.