

Pro and Con debates:

**A dual bronchodilator of LAMA & LABA
as a primary therapy for symptomatic
moderate COPD patients (나 군)**

- Con -

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정치영

Disclosure

- **I have no actual or potential conflict of interest in relation to this presentation**

Premise

There are **no clinical trial or real life data** to guide us on whether to start with bronchodilator monotherapy or dual treatment in COPD patients with group ‘L1’

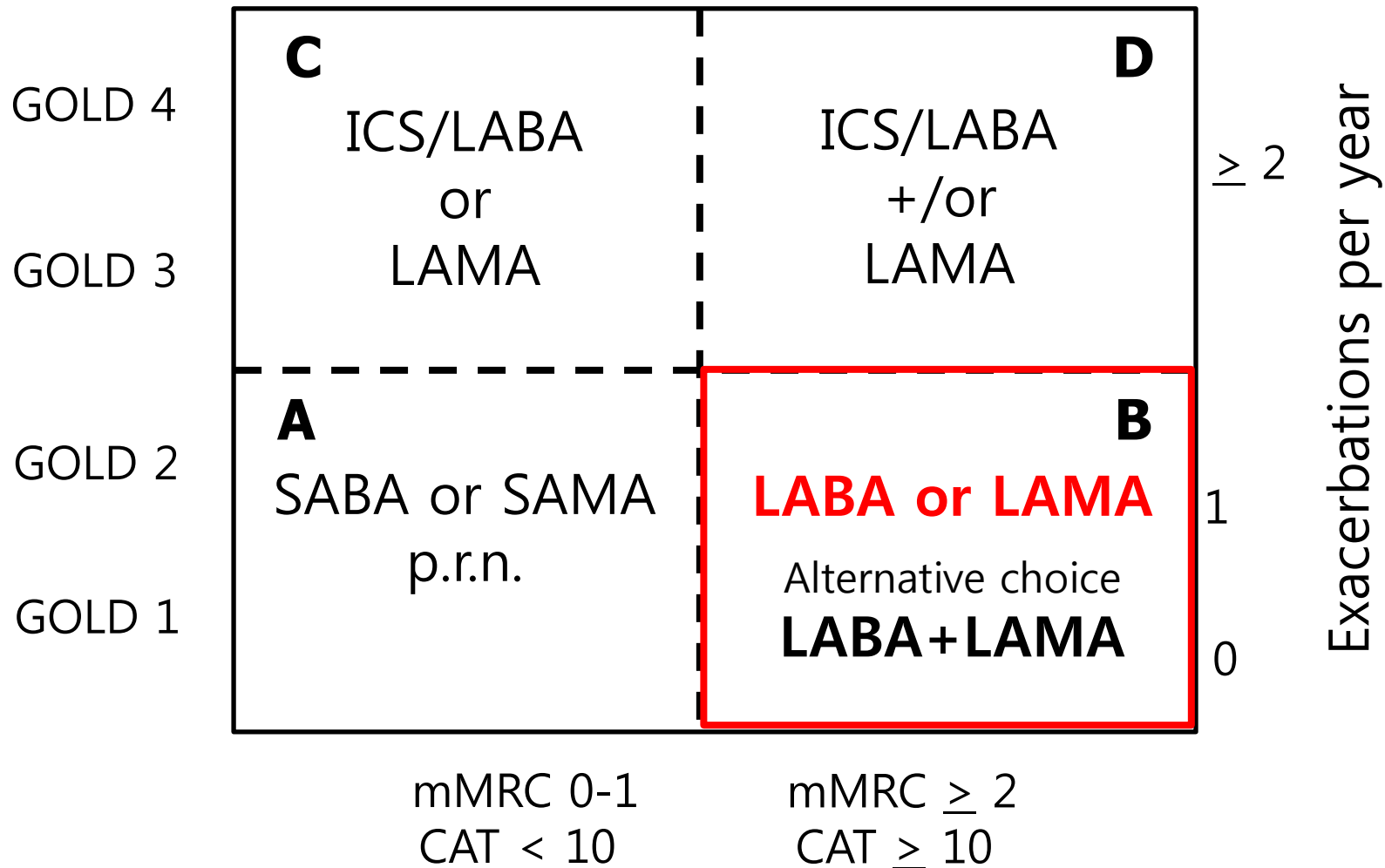
Contents

- **Current COPD guidelines**
- **Efficacy and safety of monotherapy**
- **Efficacy and safety of a dual bronchodilator**
- **Optimization vs Maximization**

Current COPD guidelines

GOLD guideline 2015

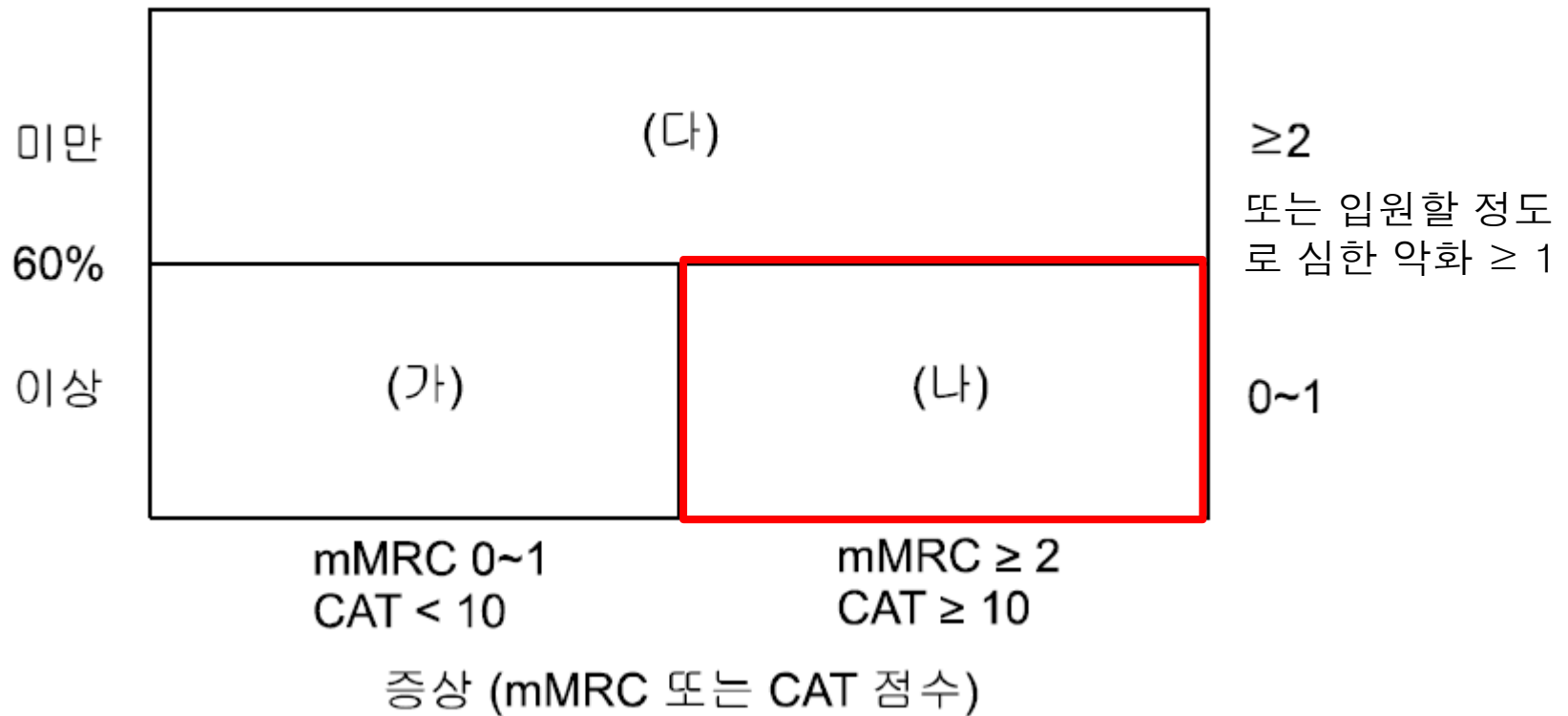
First choice



COPD 진료지침 2014

FEV1 (% 정상예측치)

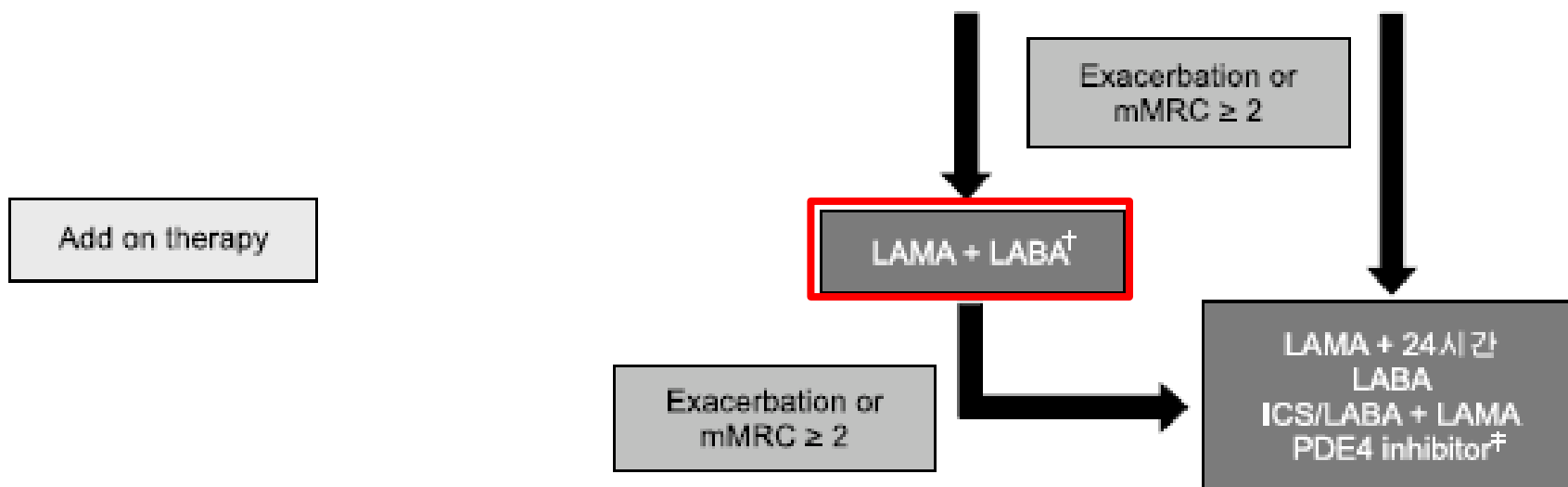
지난해 악화횟수



COPD 진료지침 2014

안정 시 COPD의 약물 단계치료

| | FEV ₁ ≥ 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-agonist as required | | |
| First choice | Short-acting beta2-agonist as required | LAMA or LABA [†] | LAMA or 24시간 LABA or ICS/LABA or LABA + LAMA |

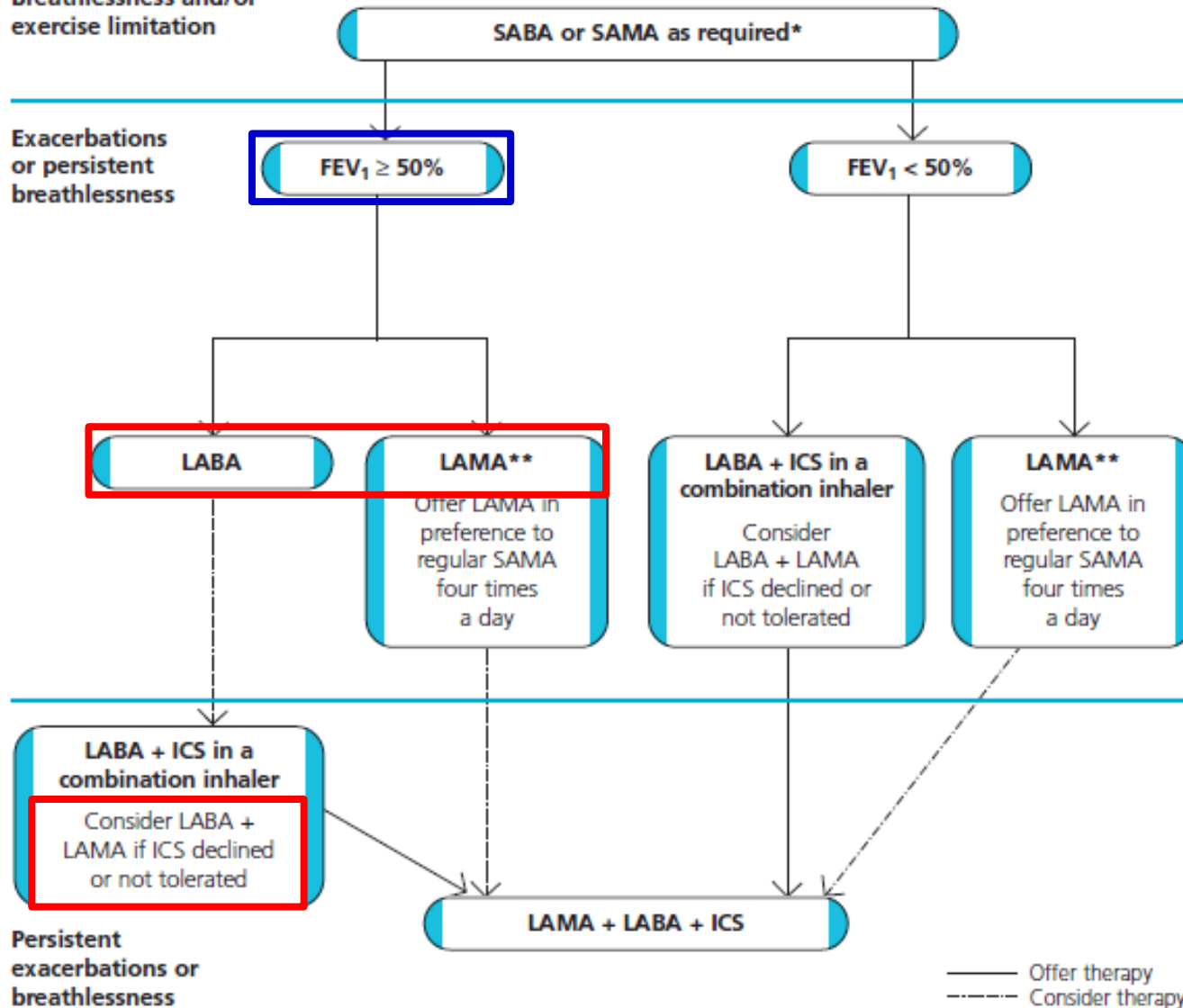


NICE guideline 2010

Inhaled therapy

Breathlessness and/or exercise limitation

Exacerbations or persistent breathlessness



Persistent exacerbations or breathlessness

Efficacy & Safety of monotherapy

Minimal clinically important difference

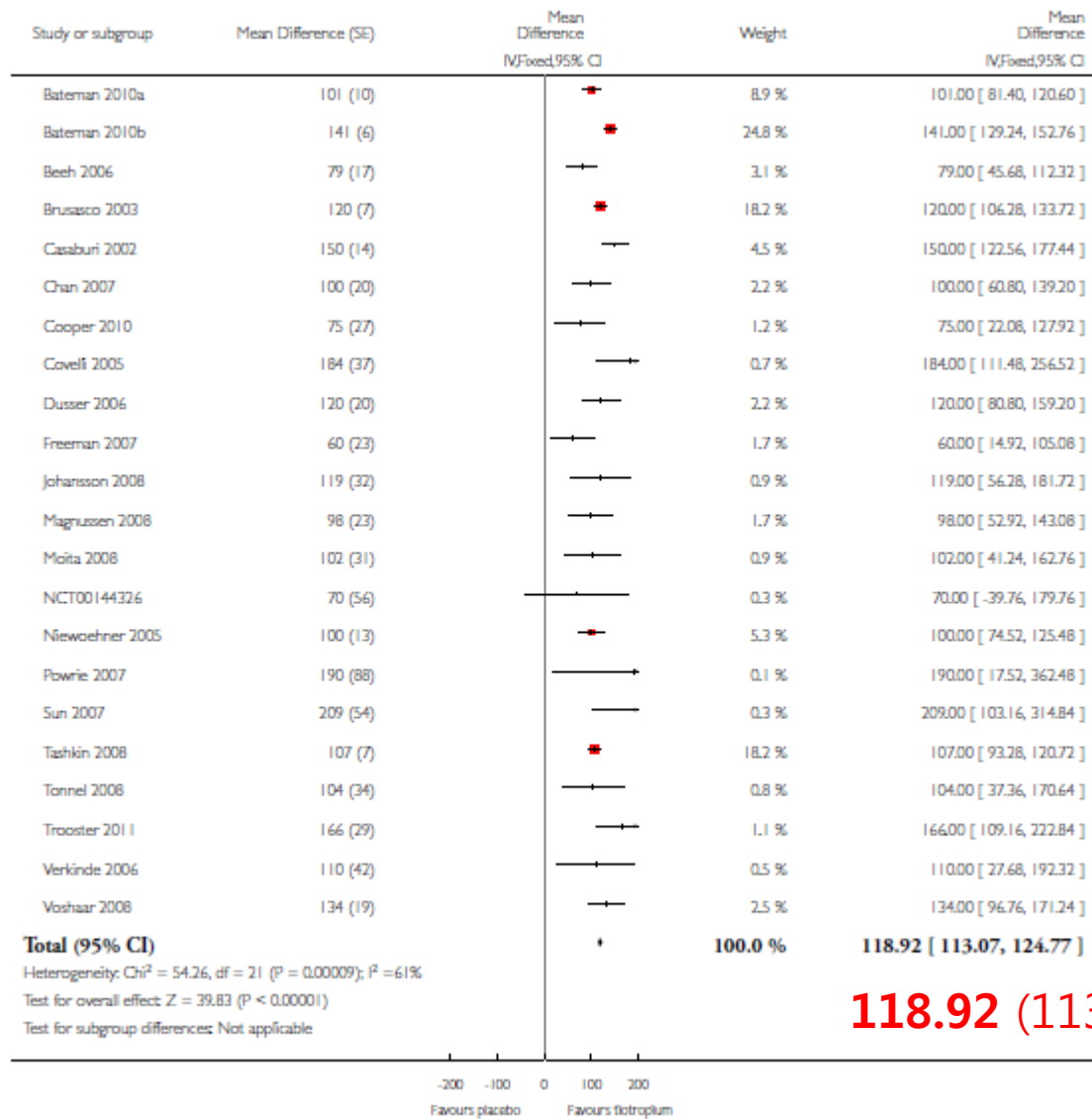
| Endpoint | MCID (improvement) |
|---|---------------------------|
| Lung function: Trough FEV1 | 100 ml |
| Dyspnea: TDI total score | 1 unit |
| Health status: SGRQ total score | 4 unit |
| Exercise capacity: Endurance shuttle walking test | 45-85 sec |

Using MCIDS to assess clinical efficacy

- Because a **MCID** is an **average estimate**, it should be used as an indicative value rather than an absolute cut-off point between benefit and no benefit
- An alternative approach to using means is to use a **responder analysis** to identify the proportion of patients who improve by more than the MCID
- **“minimum worthwhile incremental advantage”**

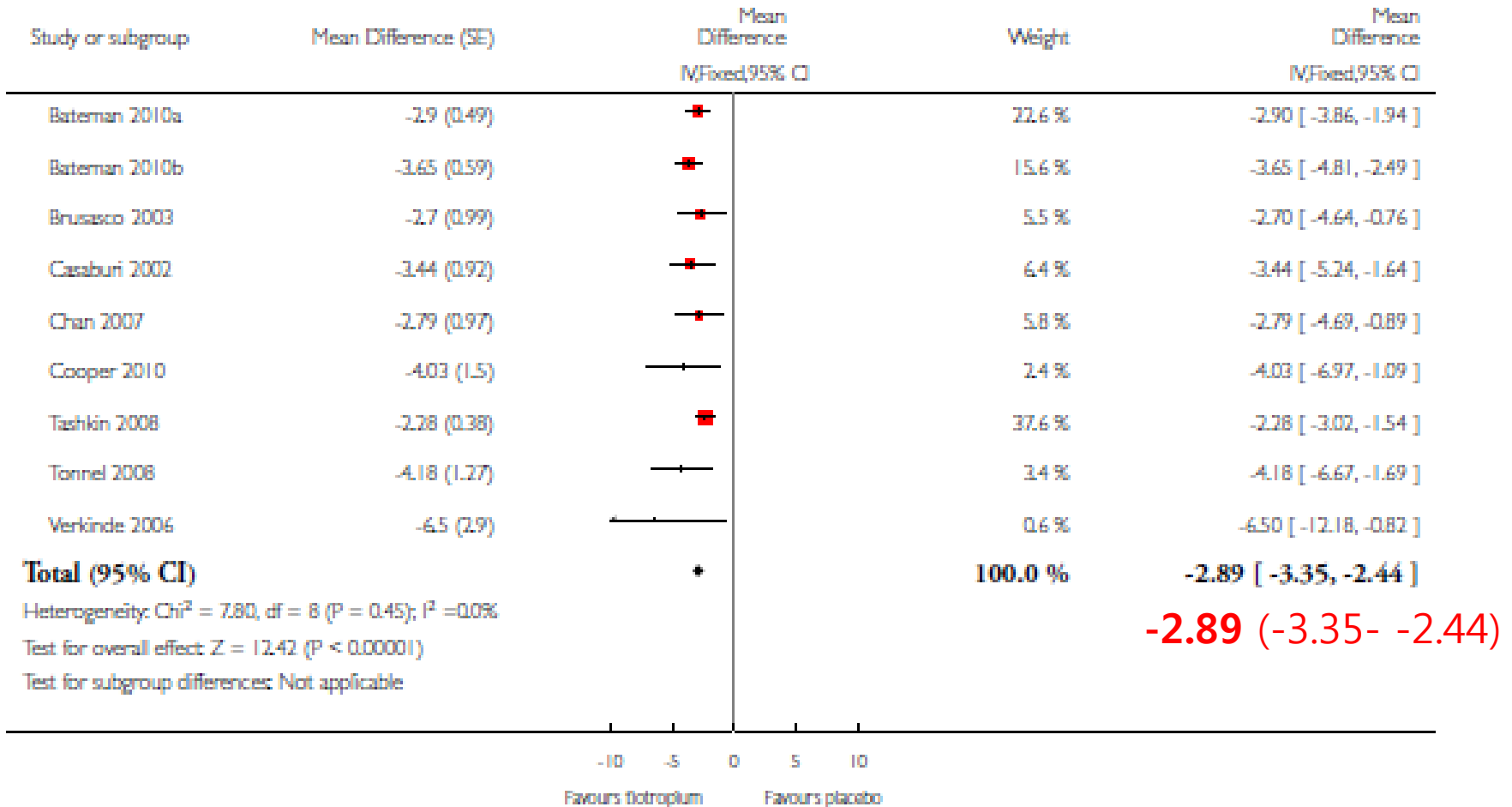
“Odds ratio”

Tiotropium vs Placebo: Trough FEV₁

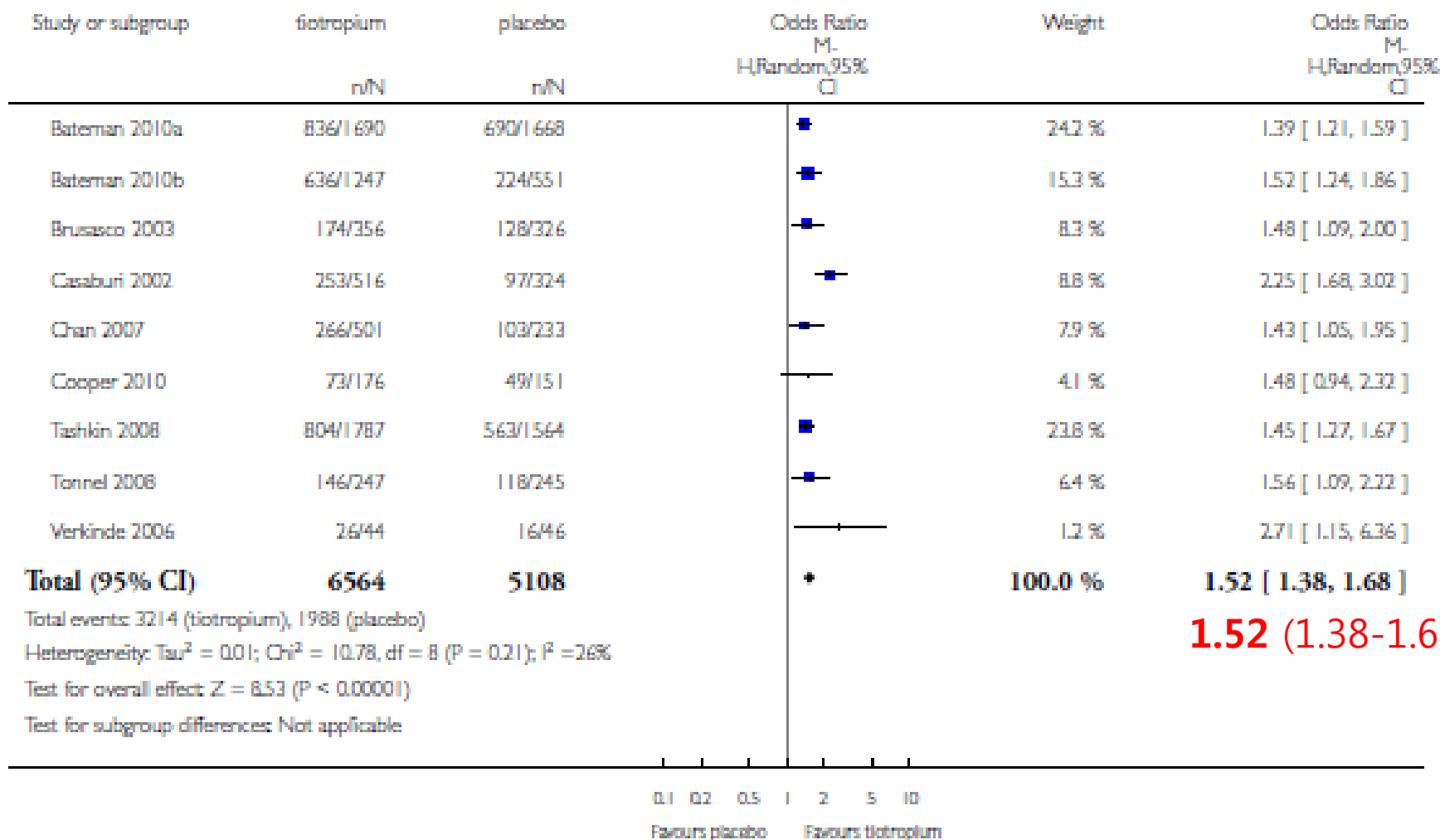


118.92 (113.07-124.77)

Tiotropium vs Placebo: SGRQ

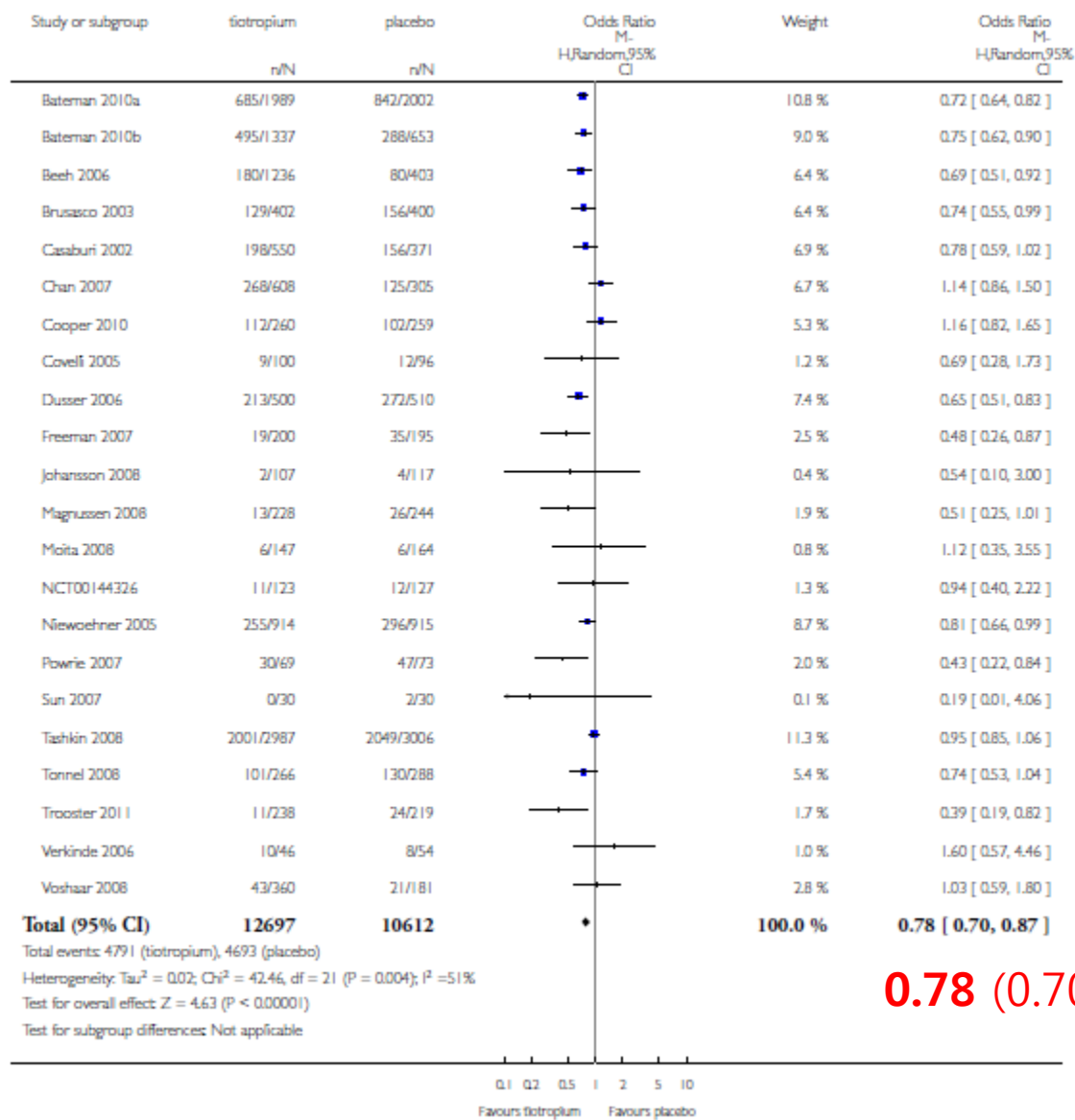


Tiotropium vs Placebo: SGRQ ≥ 4 units



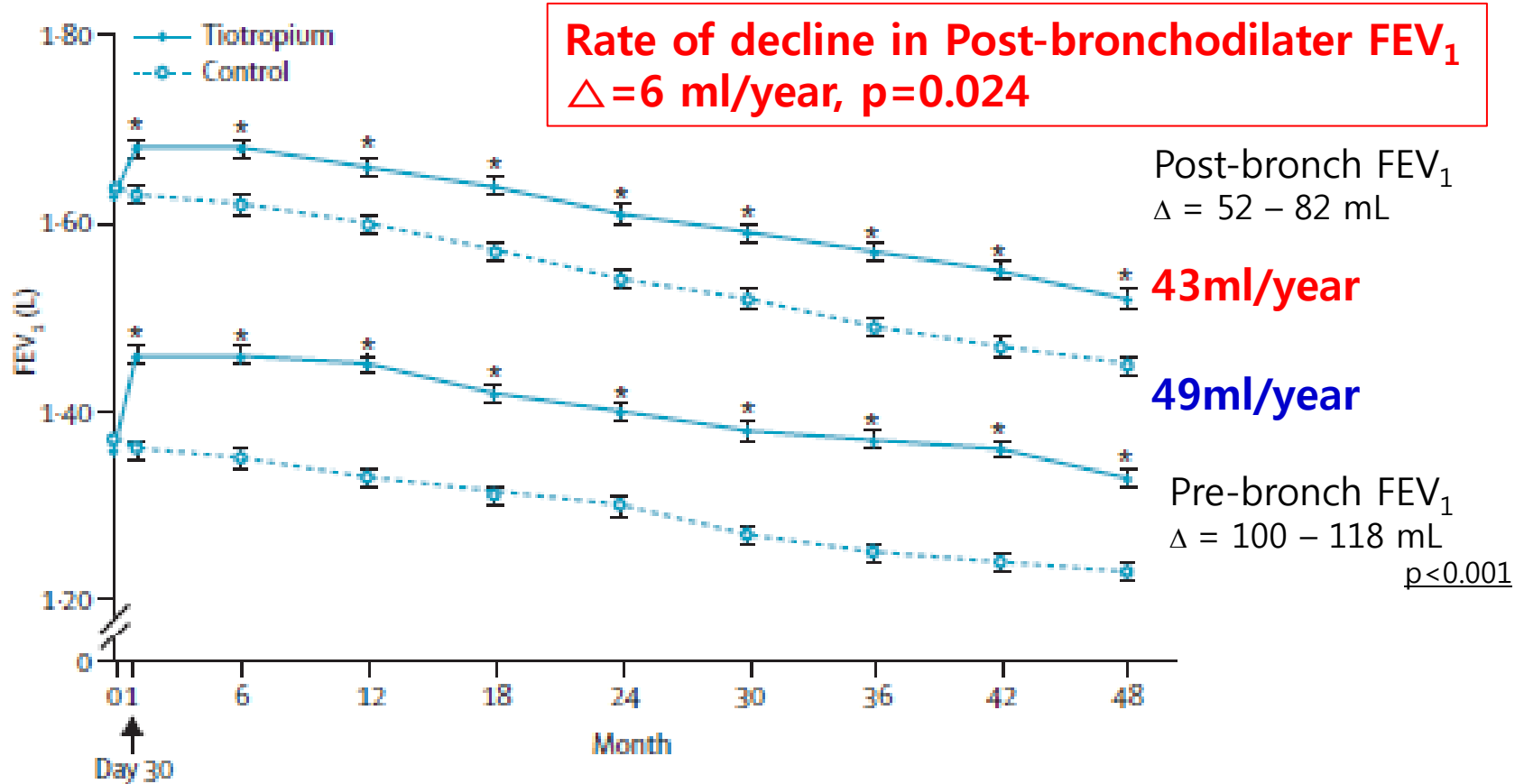
1.52 (1.38-1.68)

Tiotropium vs Placebo: Exacerbation ≥ 1



0.78 (0.70-0.87)

Tiotropium (UPLIFT): GOLD Stage II FEV₁



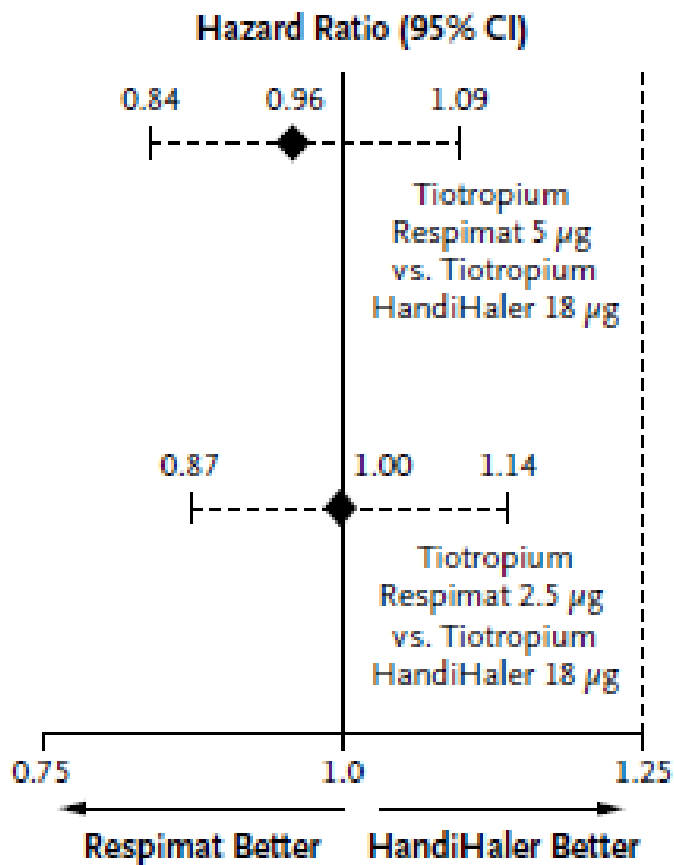
Tiotropium (UPLIFT): Adverse events

Table 4. Incidence Rate of Serious Adverse Events per 100 Patient-Years.*

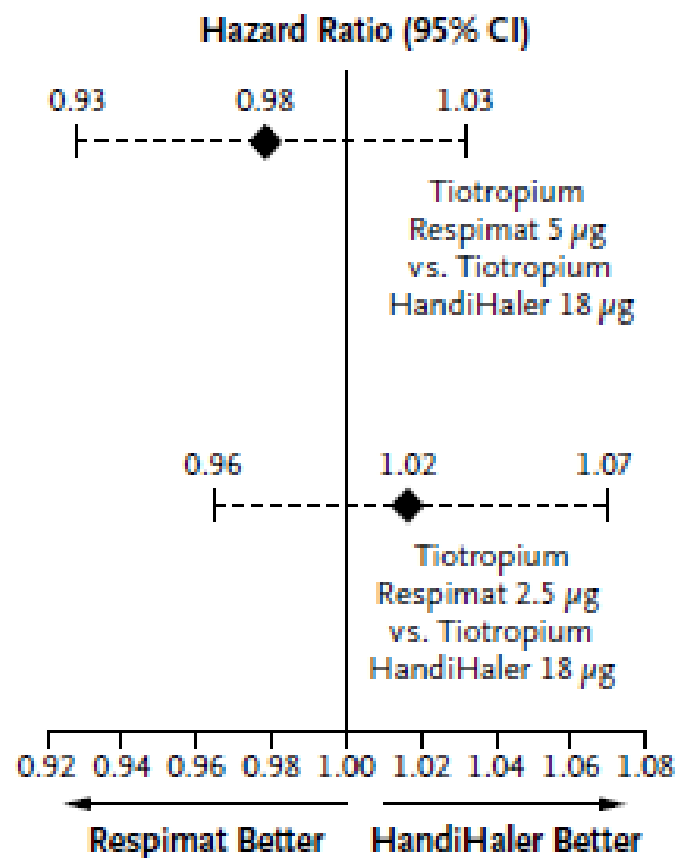
| Adverse Event | Tiotropium (N = 2986) | Placebo (N = 3006) | Relative Risk for Tiotropium vs. Placebo (95% CI) |
|--------------------------|-----------------------|--------------------|---|
| Cardiac | 3.56 | 4.21 | 0.84 (0.73–0.98) † |
| Angina | 0.51 | 0.36 | 1.44 (0.91–2.26) |
| Atrial fibrillation | 0.74 | 0.77 | 0.95 (0.68–1.33) |
| Cardiac failure | 0.61 | 0.48 | 1.25 (0.84–1.87) |
| Congestive heart failure | 0.29 | 0.48 | 0.59 (0.37–0.96) † |
| Coronary artery disease | 0.21 | 0.37 | 0.58 (0.33–1.01) |
| Myocardial infarction | 0.69 | 0.97 | 0.71 (0.52–0.99) † |
| Lower respiratory | 11.32 | 13.47 | 0.84 (0.77–0.92) † |
| Bronchitis | 0.37 | 0.31 | 1.20 (0.73–1.98) |
| COPD exacerbation | 8.19 | 9.70 | 0.84 (0.76–0.94) † |
| Dyspnea | 0.38 | 0.62 | 0.61 (0.40–0.94) † |
| Pneumonia | 3.28 | 3.46 | 0.95 (0.81–1.11) |
| Respiratory failure | 0.90 | 1.31 | 0.69 (0.52–0.92) † |

Tiotropium (TIOSPIR): Risk of death

B Death during Follow-up

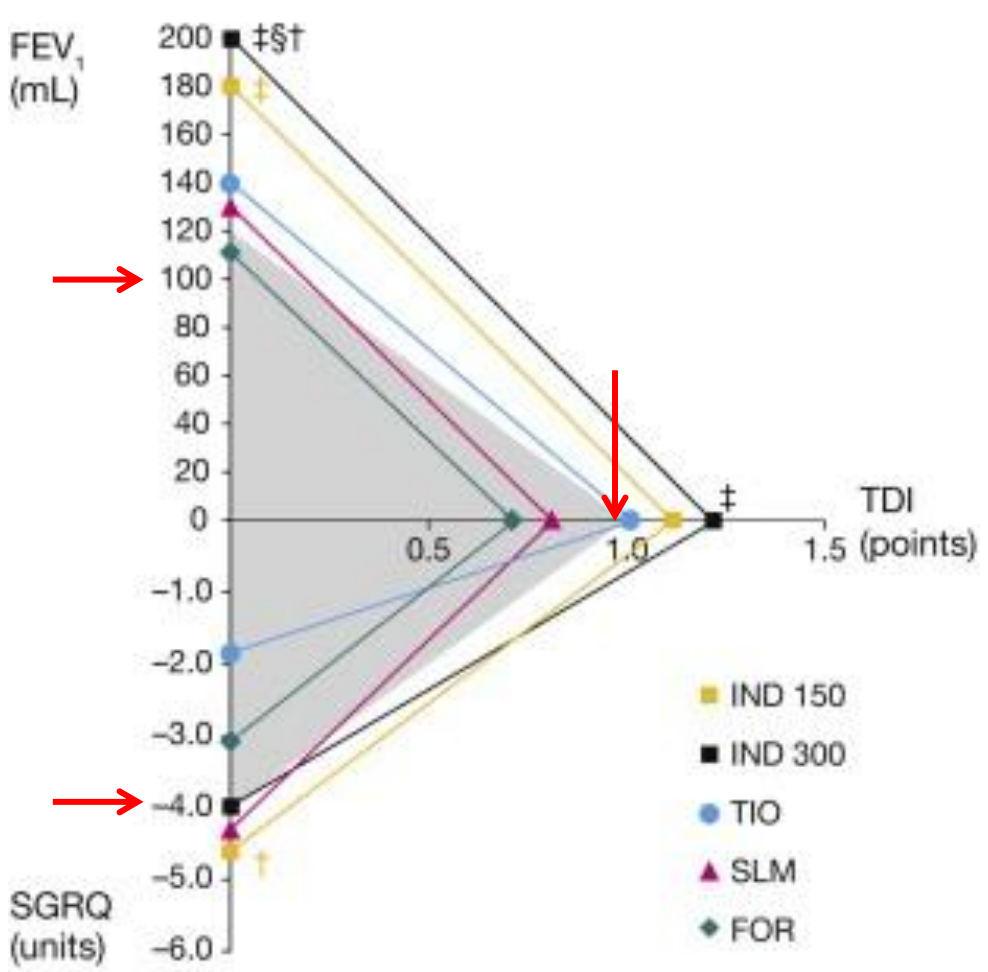


F COPD Exacerbation

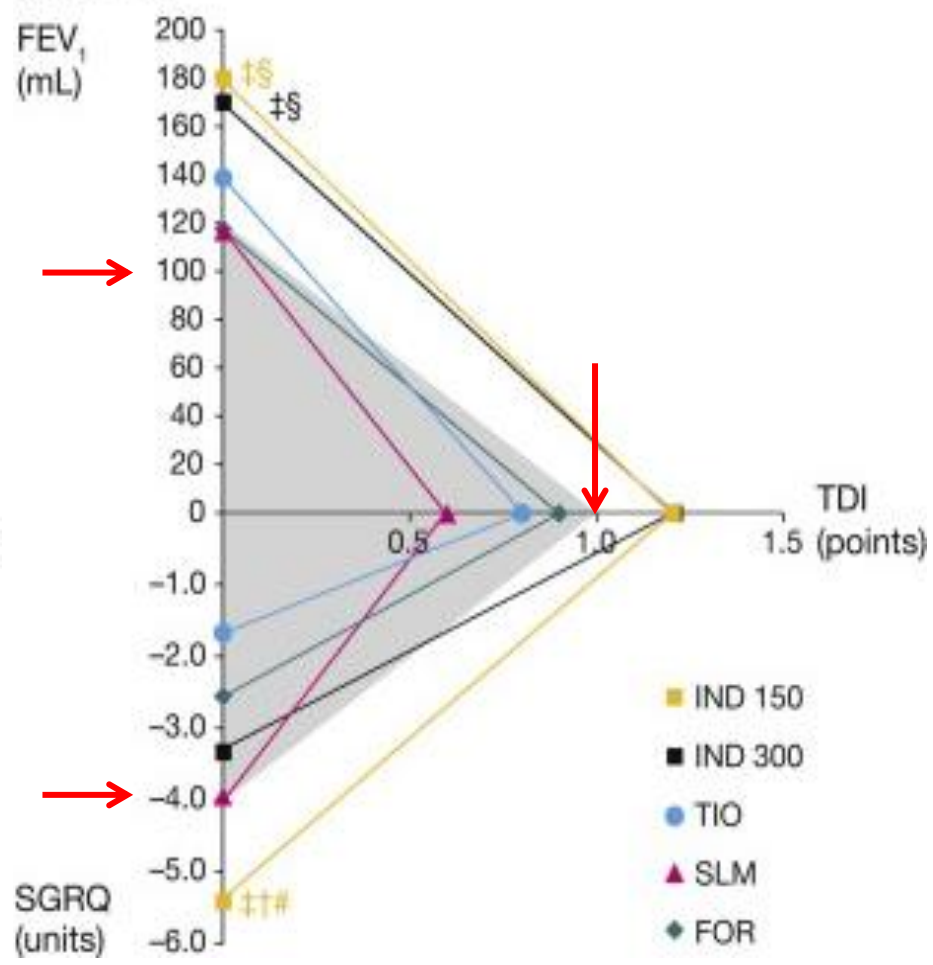


Indacaterol vs Placebo: Trough FEV₁, SGRQ, TDI

GOLD I-II



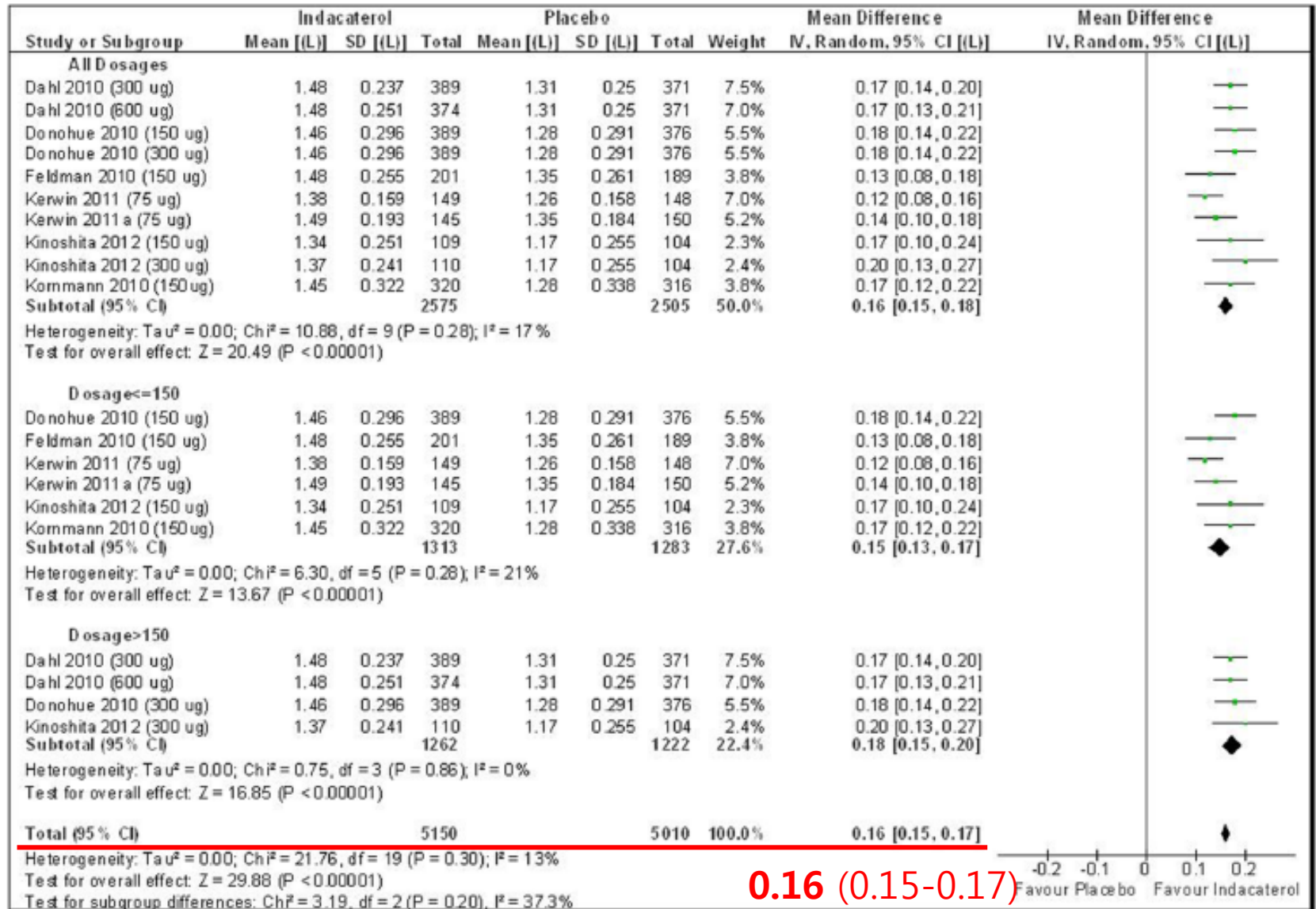
No ICS



*Pooled analysis of data from 3 randomized, placebo-controlled studies

: †vs. formoterol; §vs. salmeterol; ‡vs. tiotropium; ¶vs. indacaterol 150 µg; #vs. indacaterol 300 µg.

Indacaterol vs Placebo: FEV₁



Indacaterol: TDI

| Study (Publication Year) | Comparison | Indacaterol Group (n) | Adjusted mean (Standard error) | Control Group (n) | Adjusted mean (Standard error) | Mean difference (Standard error) |
|---|---|-----------------------|--------------------------------|-------------------|--------------------------------|----------------------------------|
| Outcome: TDI at 24th week | | | | | | |
| To et al.(2011) | Indacaterol 300ug vs Salmeterol 50ug | 118 | 0.60 (0.222) | 56 | 0.12 (0.295) | 0.48 (0.369) |
| Outcome: TDI at 26th week | | | | | | |
| Kornman et al (2010) | Indacaterol 150ug vs. Placebo | 297 | 2.03 (0.294) | 272 | 1.04 (0.300) | 0.99 (0.420) |
| Donohue et al. (2010) | Indacaterol 150ug vs. Salmeterol 50ug | 297 | 2.03 (0.294) | 289 | 2.02 (0.295) | 0.01 (0.416) |
| | Indacaterol 150ug vs. Placebo | 343 | 2.41 (0.230) | 309 | 1.40 (0.234) | 1.01 (0.328) |
| | Indacaterol 300ug vs. Placebo | 353 | 2.58 (0.226) | 309 | 1.40 (0.234) | 1.18 (0.325) |
| | Indacaterol 150ug vs. Tiotropium 18ug | 343 | 2.41 (0.230) | 349 | 2.27 (0.228) | 0.14 (0.324) |
| | Indacaterol 300ug vs. Tiotropium 18ug | 353 | 2.58 (0.226) | 349 | 2.27 (0.228) | 0.31 (0.321) |
| | Indacaterol 150ug vs. Indacaterol 300ug | 343 | 2.41 (0.230) | 353 | 2.58 (0.226) | -0.17 (0.322) |
| Outcome: TDI at 52nd week | | | | | | |
| Dahl et al (2010) | Indacaterol 300ug vs. Placebo | 317 | 2.57 (0.219) | 280 | 1.57 (0.230) | 1.00 (0.318) |
| | Indacaterol 300ug vs. Formoterol 12ug | 317 | 2.57 (0.219) | 300 | 2.28 (0.223) | 0.29 (0.313) |
| | Indacaterol 600ug vs. Placebo | 299 | 2.55 (0.222) | 280 | 1.57 (0.230) | 0.98 (0.320) |
| | Indacaterol 600ug vs. Formoterol 12ug | 299 | 2.55 (0.222) | 300 | 2.28 (0.223) | 0.27 (0.315) |
| | Indacaterol 300ug vs. Indacaterol 600ug | 317 | 2.57 (0.219) | 299 | 2.55 (0.222) | 0.02 (0.312) |
| To, et al (2011) | Indacaterol 300ug vs Salmeterol 50ug | 105 | 0.76 (0.227) | 50 | 0.57 (0.289) | 0.19 (0.367) |

Indacaterol: SGRQ

| Study (Publication Year) | Comparison | Indacaterol Group (n) | Adjusted mean (Standard error) | Control Group (n) | Adjusted mean (Standard error) | Mean difference (Standard error) |
|--|---|-----------------------|--------------------------------|-------------------|--------------------------------|----------------------------------|
| Outcome: SGRQ at 26th week | | | | | | |
| Kornmann et al.(2010) | Indacaterol 150ug vs. Placebo | 299 | 36.8 (1.04) | 274 | 41.8 (1.07) | -5.0 (1.49) |
| | Indacaterol 150ug vs. Salmeterol 50ug | 299 | 36.8 (1.04) | 292 | 37.8 (1.05) | -1.0 (1.48) |
| Donohue et al.(2010) | Indacaterol 150ug vs. Placebo | 346 | 37.1 (0.78) | 319 | 40.4 (0.79) | -3.3 (1.11) |
| | Indacaterol 300ug vs. Placebo | 360 | 38.0 (0.76) | 319 | 40.4 (0.79) | -2.4 (1.10) |
| | Indacaterol 150ug vs. Tiotropium 18ug | 346 | 37.1 (0.78) | 357 | 39.4 (0.76) | -2.3 (1.09) |
| | Indacaterol 300ug vs. Tiotropium 18ug | 360 | 38.0 (0.76) | 357 | 39.4 (0.76) | -1.4 (1.07) |
| | Indacaterol 150ug vs. Indacaterol 300ug | 346 | 37.1 (0.78) | 360 | 38.0 (0.76) | -0.9 (1.09) |
| Outcome: SGRQ at 52nd week | | | | | | |
| Dahl et al.(2010) | Indacaterol 300ug vs. Placebo | 322 | 36.5 (0.82) | 280 | 41.3 (0.87) | -4.8 (1.20) |
| | Indacaterol 300ug vs. Formoterol 12ug | 322 | 36.5 (0.82) | 302 | 37.3 (0.84) | -0.8 (1.17) |
| | Indacatero 600ug vs. Placebo | 305 | 36.6 (0.83) | 280 | 41.3 (0.87) | -4.7 (1.20) |
| | Indacaterol 600ug vs. Formoterol 12ug | 305 | 36.6 (0.83) | 302 | 37.3 (0.84) | -0.7 (1.18) |
| | Indacaterol 300ug vs. Indacaterol 600ug | 322 | 36.5 (0.82) | 305 | 36.6 (0.83) | -0.1 (1.17) |

Indacaterol: Adverse events

Table 6 Deaths and serious (fatal and nonfatal) adverse events, with listing of most common serious adverse events (incidence \geq 0.005 per patient-year in indacaterol 150 μ g group), adjusted for length of time on treatment

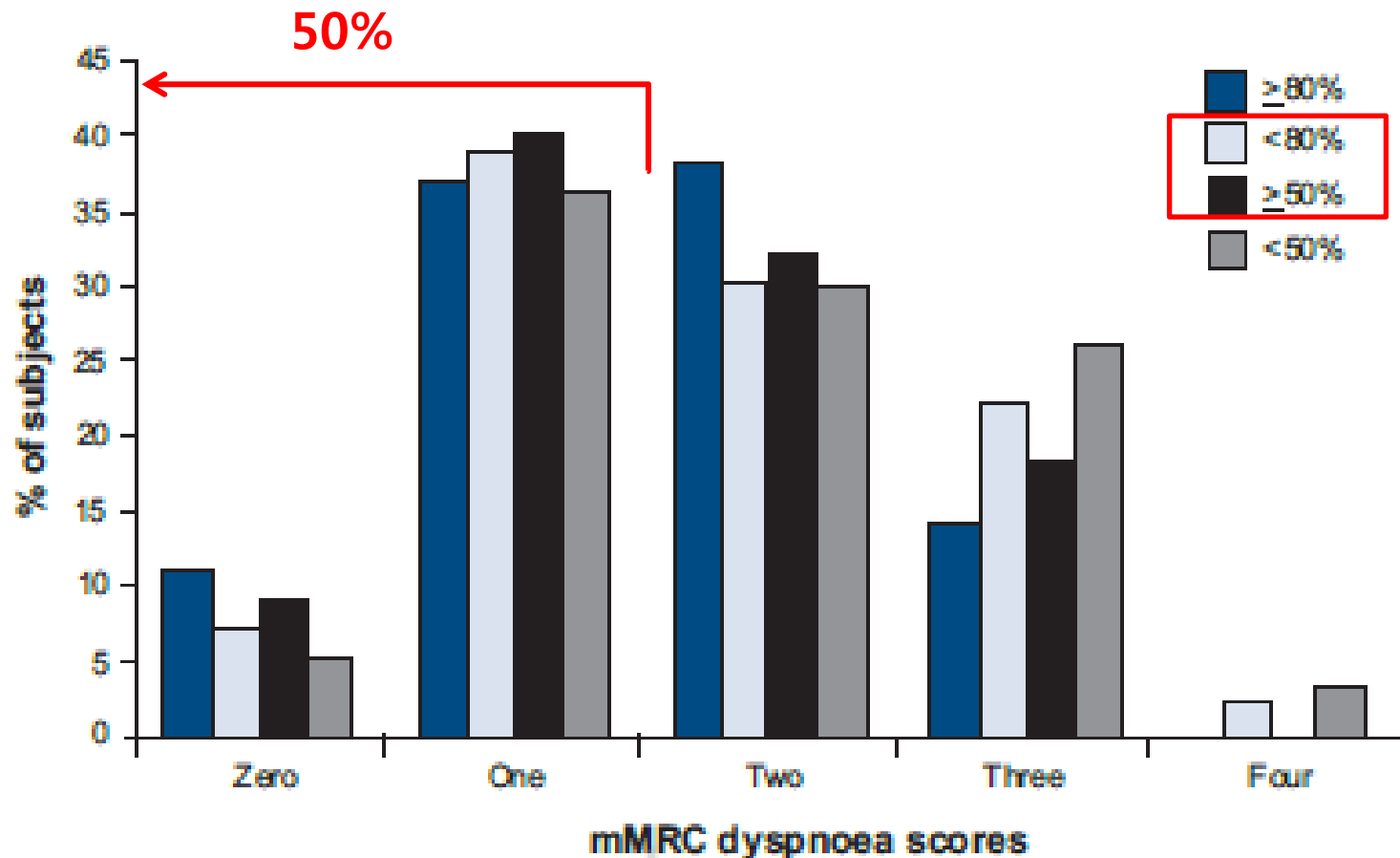
| | IND 75 n = 449 | IND 150 n = 2611 | IND 300 n = 1157 | IND 600 n = 547 | FOR n = 556 | SLM n = 895 | TIO n = 1214 | PBO n = 2012 |
|--|-------------------|---------------------|---------------------|--------------------|----------------|----------------|-----------------|-----------------|
| Total patient years | 105.06 | 859.72 | 736.97 | 394.49 | 396.21 | 274.93 | 357.97 | 923.60 |
| Deaths (n) | 0 | 4 | 2 | 1 | 4 | 1 | 4 | 14 |
| Deaths (n per patient year) | 0 | 0.01 | 0 | 0 | 0.01 | 0 | 0.01 | 0.02 |
| Serious adverse events (fatal and nonfatal) (n per patient year) | 0.25 | 0.24 | 0.24 | 0.21 | 0.32 | 0.18 | 0.33 | 0.27 |
| Respiratory, thoracic and mediastinal disorders (total) | 0.07 | 0.05 | 0.09 | 0.04 | 0.12 | 0.06 | 0.06 | 0.09 |
| COPD worsening | 0.05 | 0.05 | 0.06 | 0.03 | 0.10 | 0.04 | 0.04 | 0.07 |
| – leading to hospitalization | 0.05 | 0.05 | 0.06 | 0.03 | 0.09 | 0.04 | 0.04 | 0.06 |
| – in patients on ICS | 0.05 | 0.07 | 0.08 | 0.03 | 0.09 | 0.05 | 0.04 | 0.08 |
| – in patients not on ICS | 0.05 | 0.03 | 0.04 | 0.04 | 0.11 | 0.03 | 0.04 | 0.05 |
| Infections and infestations (total) | 0.05 | 0.04 | 0.04 | 0.02 | 0.08 | 0.04 | 0.05 | 0.05 |
| Pneumonia | 0.02 | 0.01 | 0.01 | 0.01 | 0.02 | 0.01 | 0.02 | 0.01 |
| Lower RTI | 0 | 0.01 | 0 | 0.01 | 0.01 | 0.01 | 0 | 0.01 |
| URTI bacterial | 0.01 | 0.01 | 0 | 0 | 0.01 | 0.01 | 0 | 0.01 |
| Cardiac disorders (total) | 0.04 | 0.03 | 0.03 | 0.03 | 0.02 | 0.03 | 0.05 | 0.03 |
| Angina pectoris | 0.01 | 0.01 | 0 | 0 | 0 | 0 | 0 | 0 |
| Acute myocardial infarction | 0 | 0.01 | 0 | 0 | 0 | 0 | 0 | 0 |
| Atrial fibrillation | 0.01 | 0.01 | 0.01 | 0 | 0 | 0 | 0.01 | 0.01 |

Abbreviations: IND, indacaterol; FOR, formoterol; SLM, salmeterol; TIO, tiotropium; PBO, placebo; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; RTI, respiratory tract infection; URTI, upper RTI; n, number.

Indacaterol (meta-analysis): Adverse events

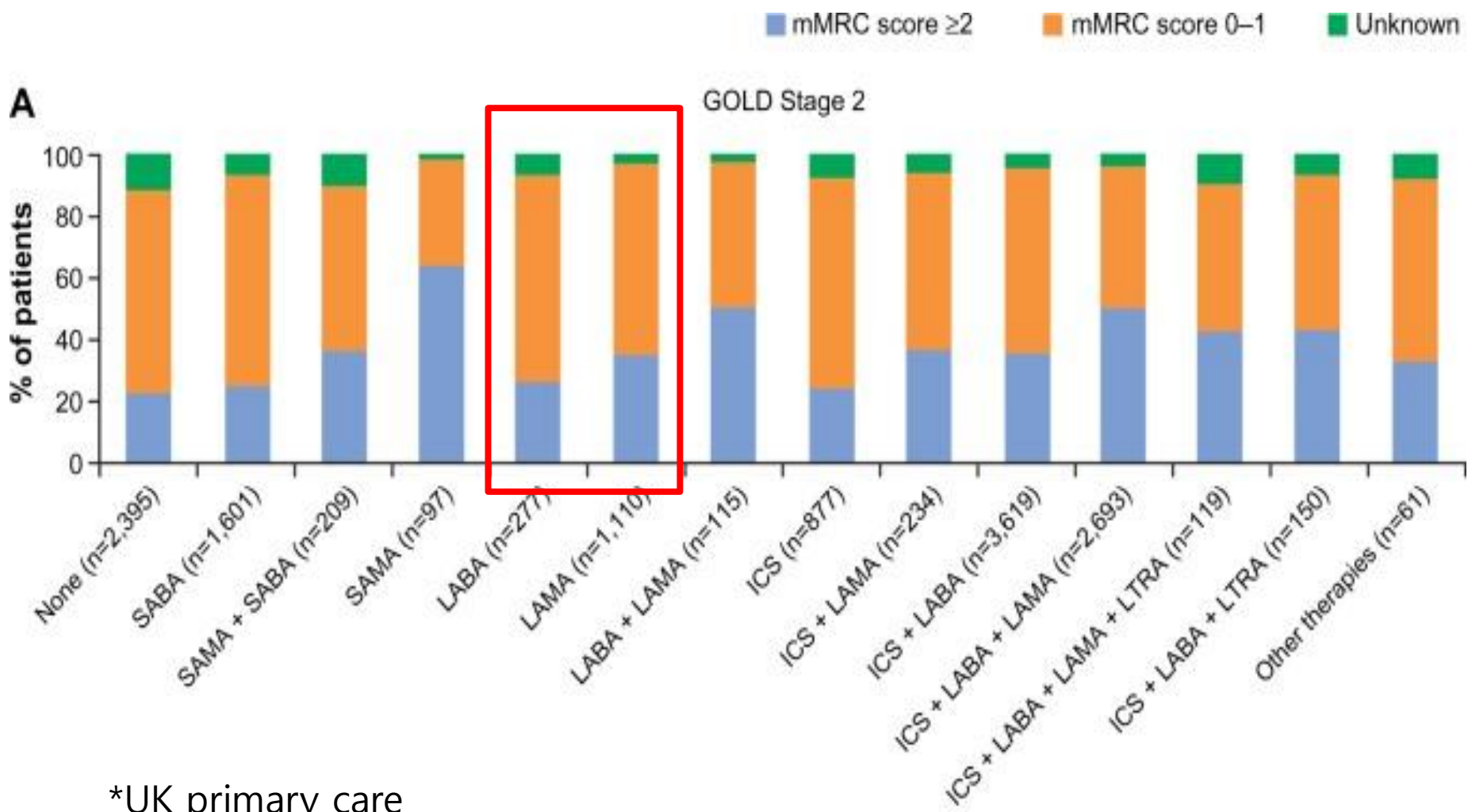
| Events | No. of studies | Event/Total | Event/Total | Combined Effect | | Heterogeneity |
|-----------------------------------|----------------|-------------|-------------|-------------------|----------|--------------------|
| | | | | RR (95% CI) | P -value | I ² (%) |
| Any dose | | | | | | |
| Any reported adverse events | 10 | 1673/2787 | 1595/2793 | 1.05 (1.00, 1.10) | 0.05 | 19% |
| Serious adverse events | 8 | 120/1925 | 132/1929 | 0.92 (0.73, 1.17) | 0.52 | 0% |
| Upper respiratory tract infection | 7 | 148/2254 | 156/2269 | 0.96 (0.73, 1.27) | 0.79 | 31% |
| Nasopharyngitis | 9 | 285/2576 | 232/2588 | 1.22 (1.01, 1.47) | 0.04 | 15% |
| Cough | 10 | 178/2787 | 152/2793 | 1.16 (0.91, 1.46) | 0.22 | 14% |
| Indacaterol ≤150 ug | | | | | | |
| Any reported adverse events | 6 | 757/1393 | 726/1394 | 1.04(0.97–1.12) | 0.23 | 0% |
| Serious adverse events | 6 | 86/1393 | 91/1394 | 0.96 (0.72–1.27) | 0.76 | 0% |
| Upper respiratory tract infection | 3 | 65/860 | 48/870 | 1.35(0.94–1.95) | 0.10 | 0% |
| Nasopharyngitis | 5 | 85/1182 | 73/1189 | 1.24(0.80–1.91) | 0.33 | 37% |
| Cough | 6 | 78/1393 | 71/1394 | 1.09(0.74–1.61) | 0.65 | 24% |
| Indacaterol >150 ug | | | | | | |
| Any adverse events | 4 | 916/1394 | 869/1399 | 1.05(0.96–1.15) | 0.32 | 56% |
| Serious adverse events | 2 | 34/532 | 41/535 | 0.75(0.34–1.66) | 0.47 | 30% |
| Upper respiratory tract infection | 4 | 83/1394 | 108/1399 | 0.77(0.59–1.02) | 0.07 | 0% |
| Nasopharyngitis | 4 | 200/1394 | 159/1399 | 1.27(1.04–1.54) | 0.02 | 0% |
| Cough | 4 | 100/1394 | 81/1399 | 1.23(0.90–1.68) | 0.20 | 16% |

mMRC dyspnea scores in COPD with monotherapy



* Patients: FEV1/FVC ≤ 0.70 (n=689)
regularly taking only one long-acting bronchodilator

mMRC dyspnea scores in COPD GOLD 2 stage



*UK primary care
 total 24,957, GOLD B 4651, GOLD 2 stage 13557

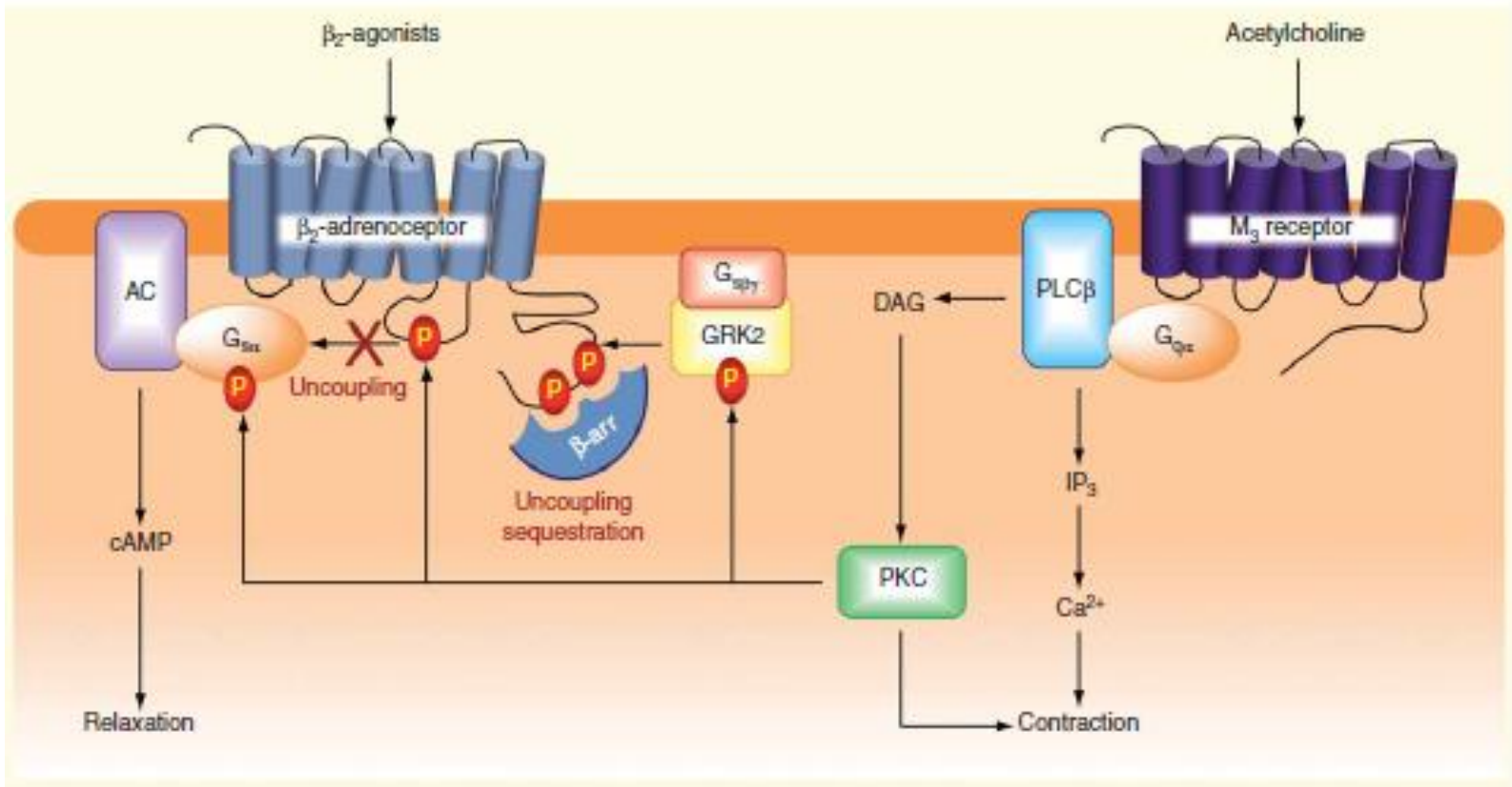


Efficacy & Safety of a dual bronchodilator

Novel LAMA/LABA fixed dose combinations for COPD

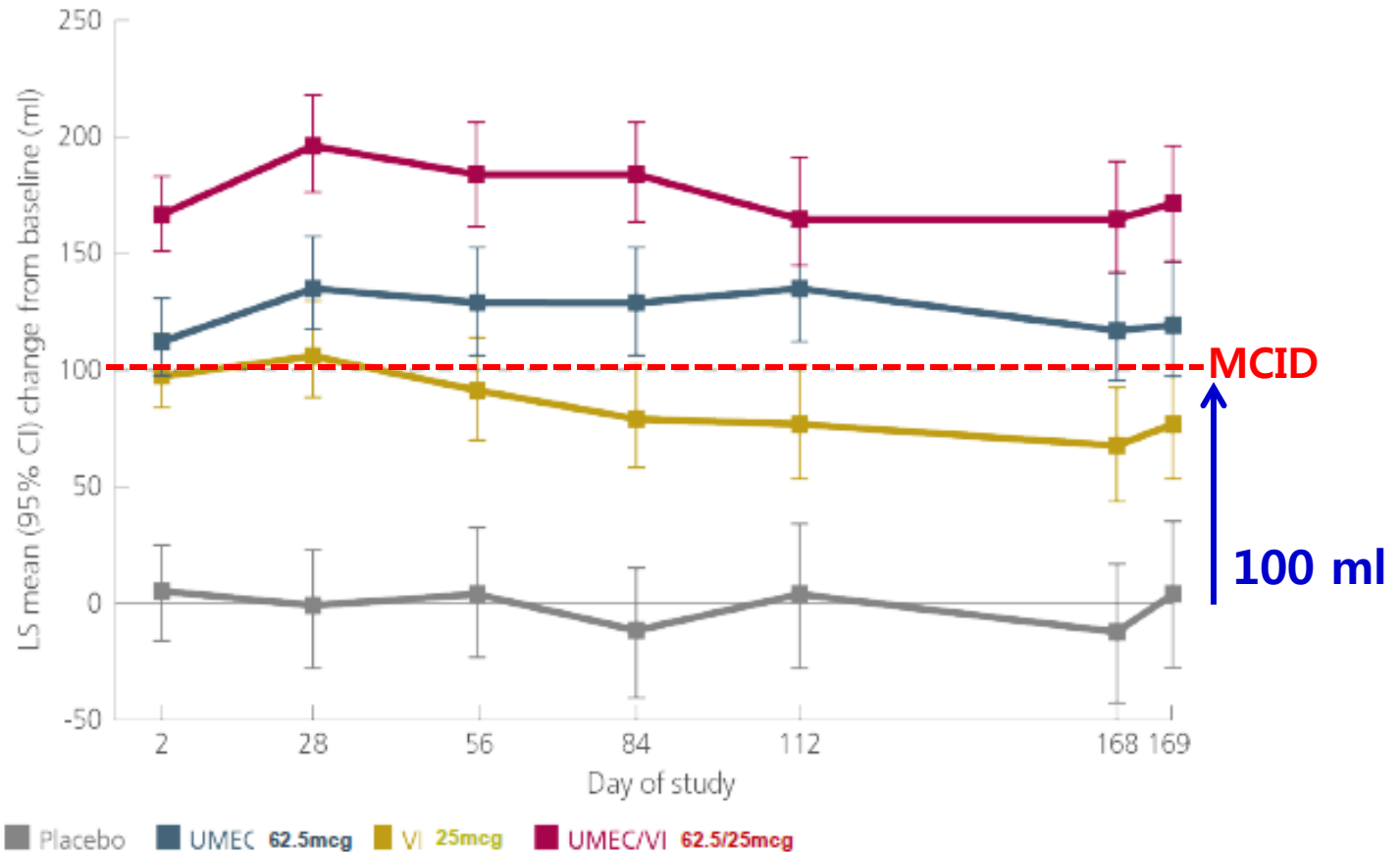
| Combination | Dosing | Device | Manufacturer |
|--|-------------|------------|--------------------------------|
| Glycopyrronium/ Indacaterol | Once daily | Breezhaler | Novartis |
| Umeclidinium/ Vilanterol | Once daily | Ellipta | GlaxoSmithKline/Theravance |
| Acridinium/ Formoterol | Twice daily | Genuair | Almirall/Forest |
| Tiotropium/ Olodaterol | Once daily | Respimat | Boehringer Ingelheim |
| Glycopyrrolate/ Formoterol | Twice daily | HFA MDI | PearlTherapeutics/ AstraZeneca |

Dual bronchodilator induced by LAMA/LABA FDC



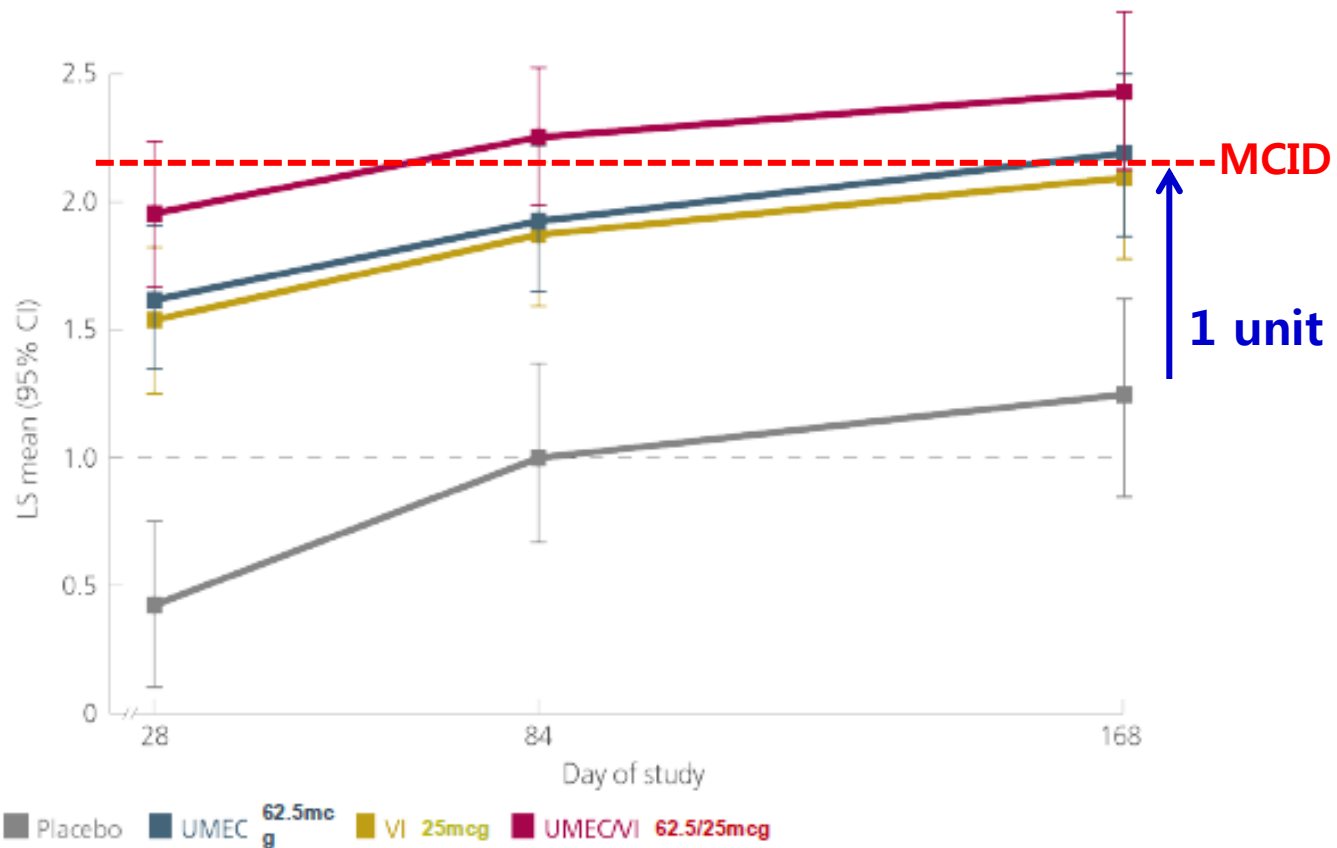
UMEC/VI (3373): Trough FEV₁ on day 169

Mean change from baseline in trough FEV₁^{1,2}



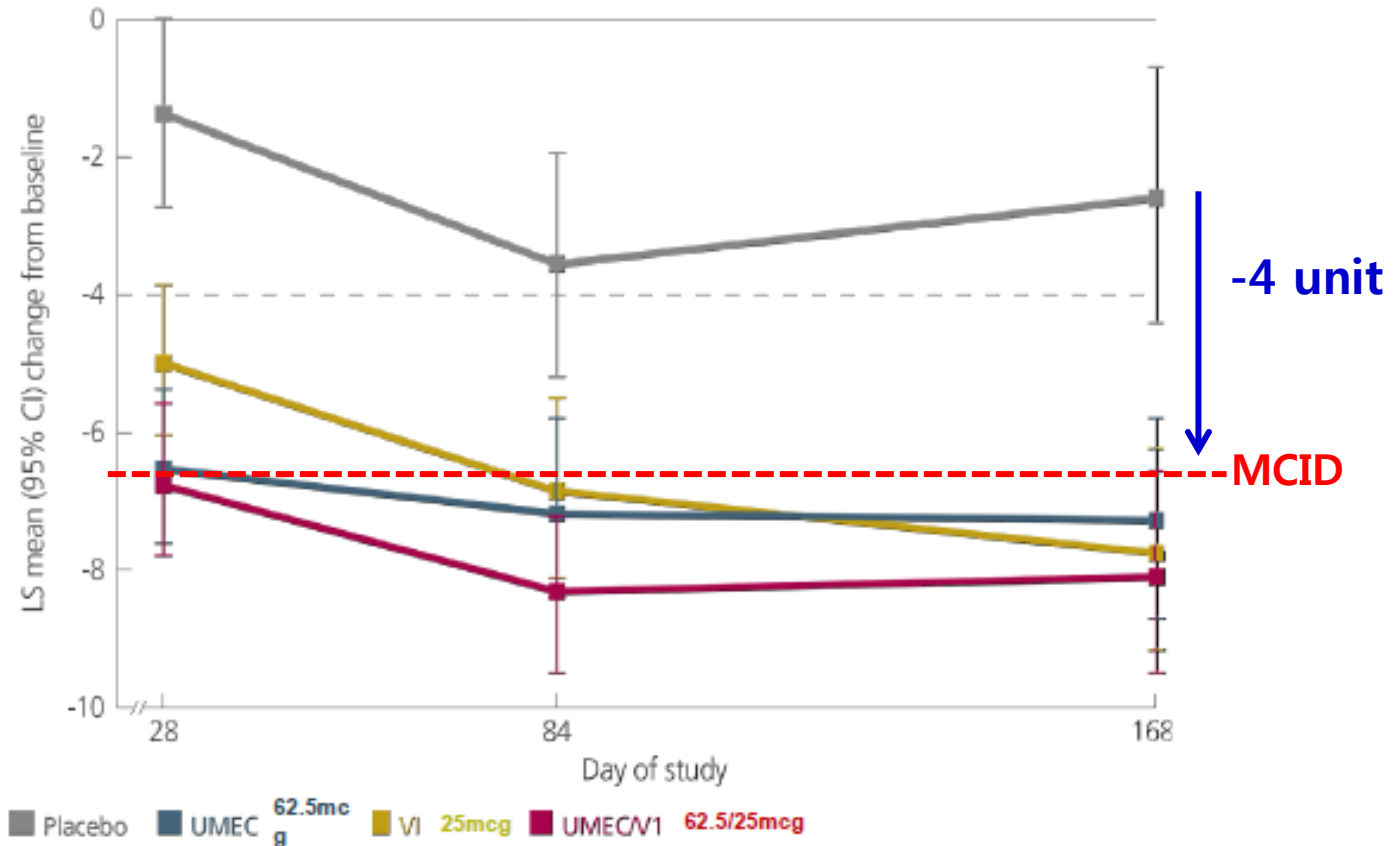
UMEC/VI (3373): TDI focal score at week 24

Mean Transition Dyspnoea Index (TDI) focal score^{1,2}



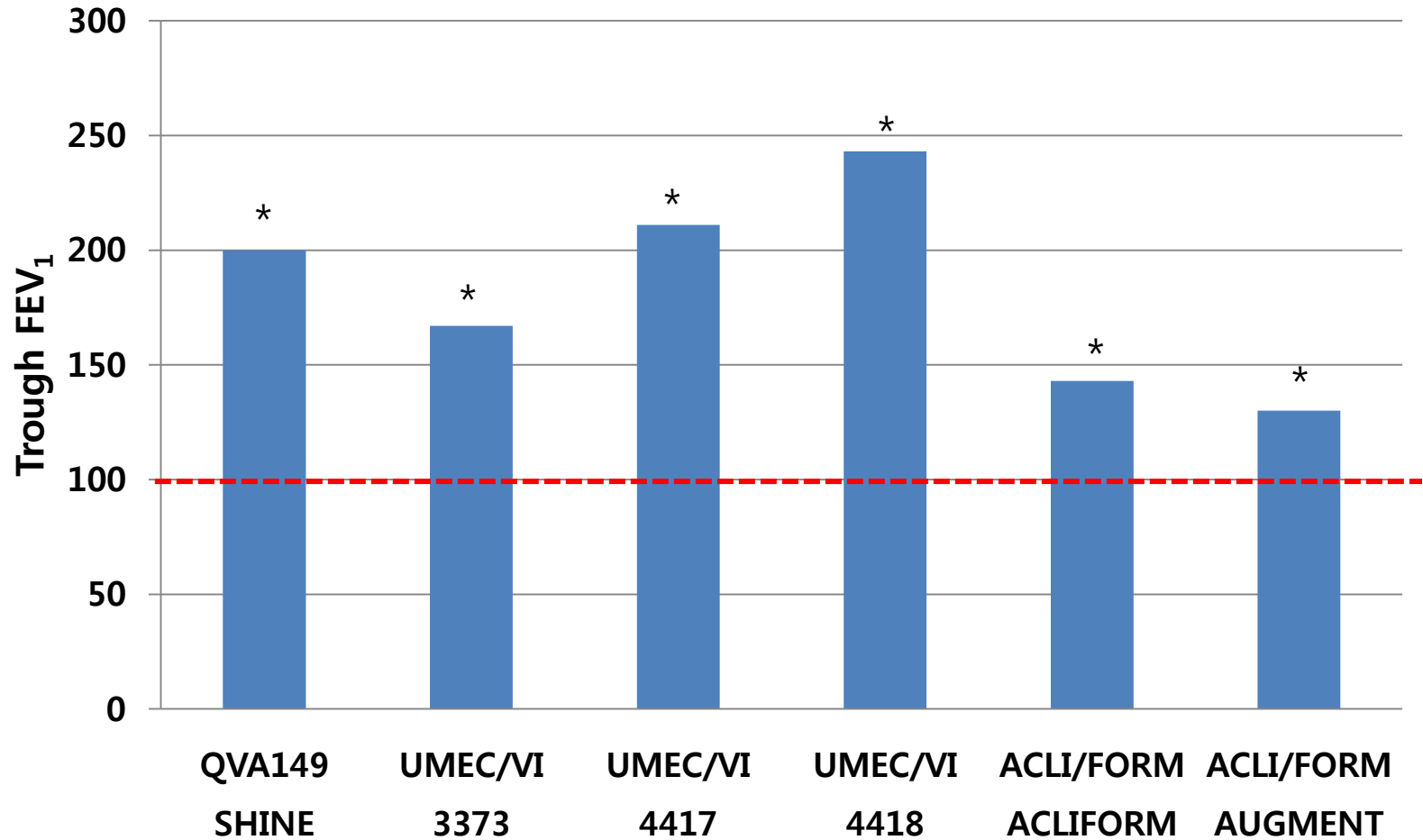
Proportion of responders: odds ratio 1.6, 1.5, 2.0

UMEC/VI (3373): SGRQ total score at week 24



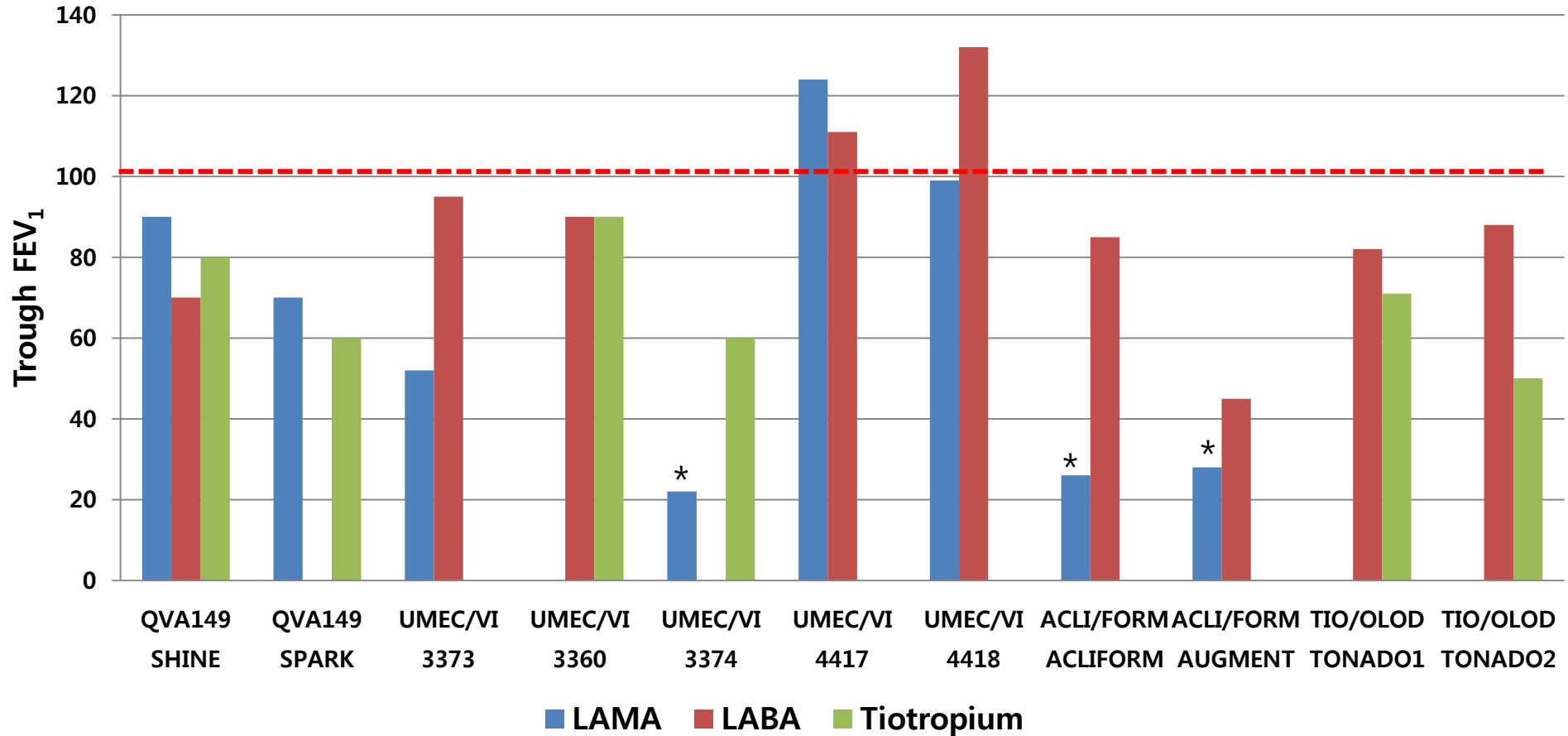
Proportion of responders: odds ratio 1.6, 1.9, 2.0

LABA/LAMA FDC vs Placebo: Trough FEV₁



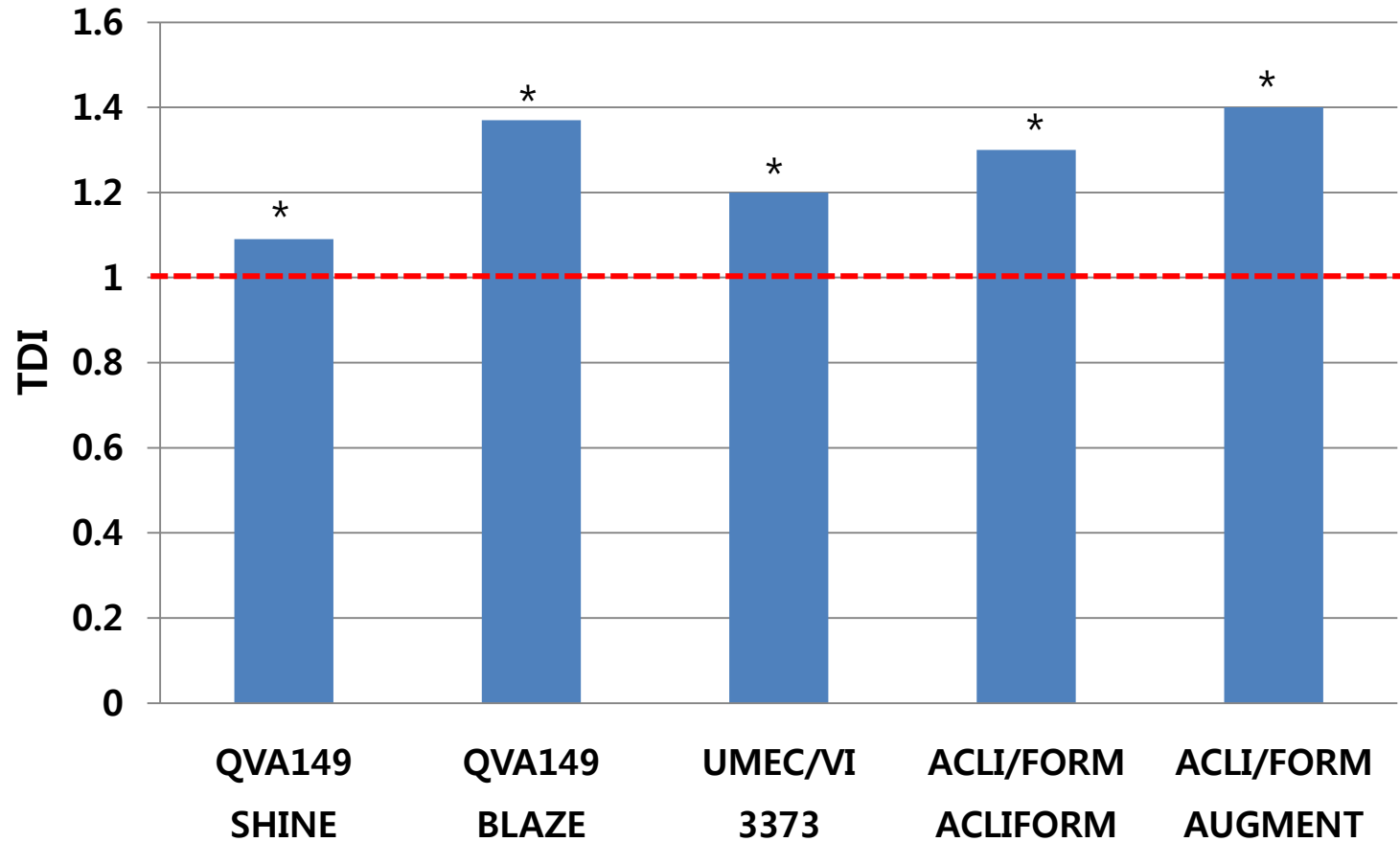
*p<0.001

LABA/LAMA FDC vs Monotherapy: Trough FEV₁



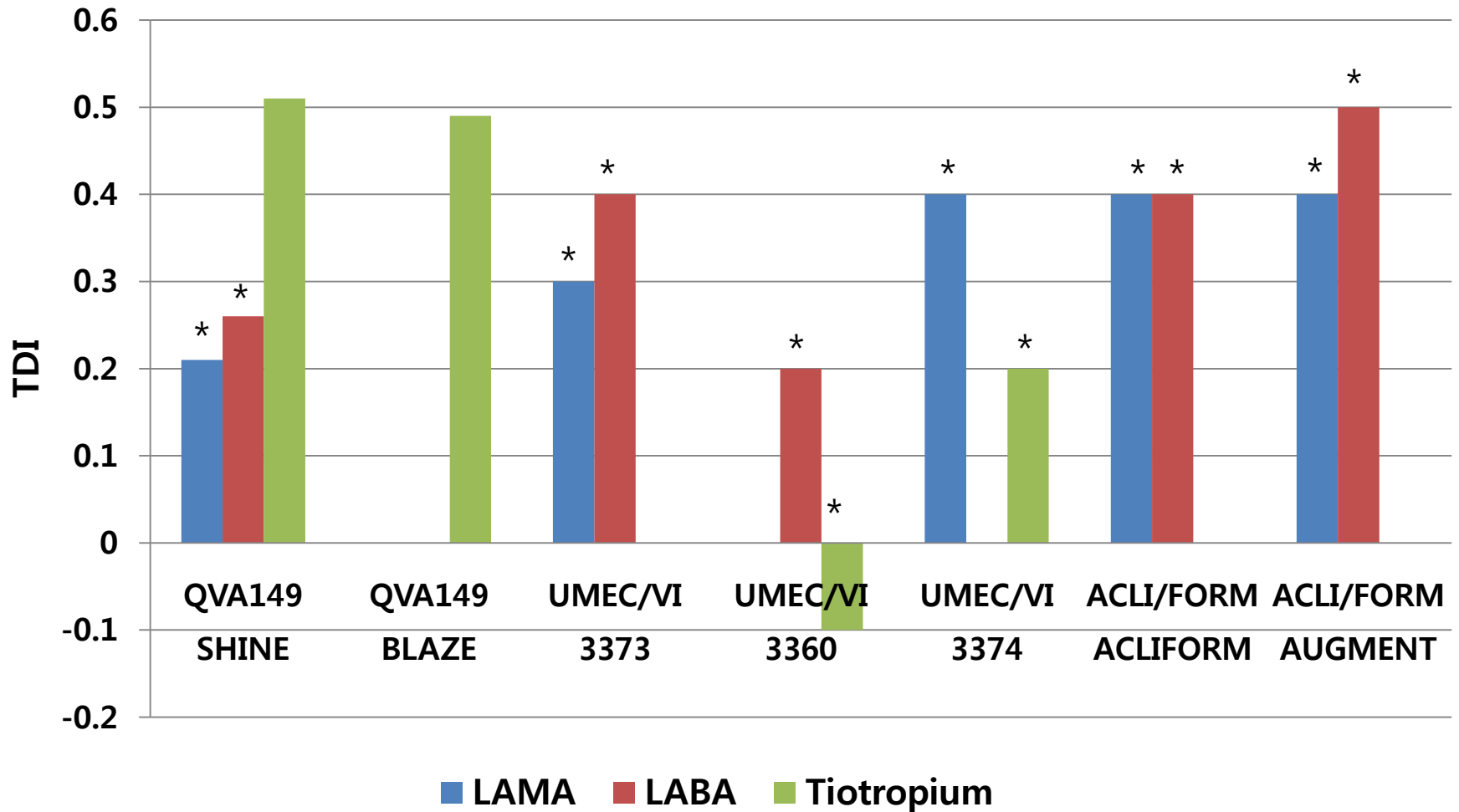
***Not statistically significant**

LABA/LAMA FDC vs Placebo: TDI



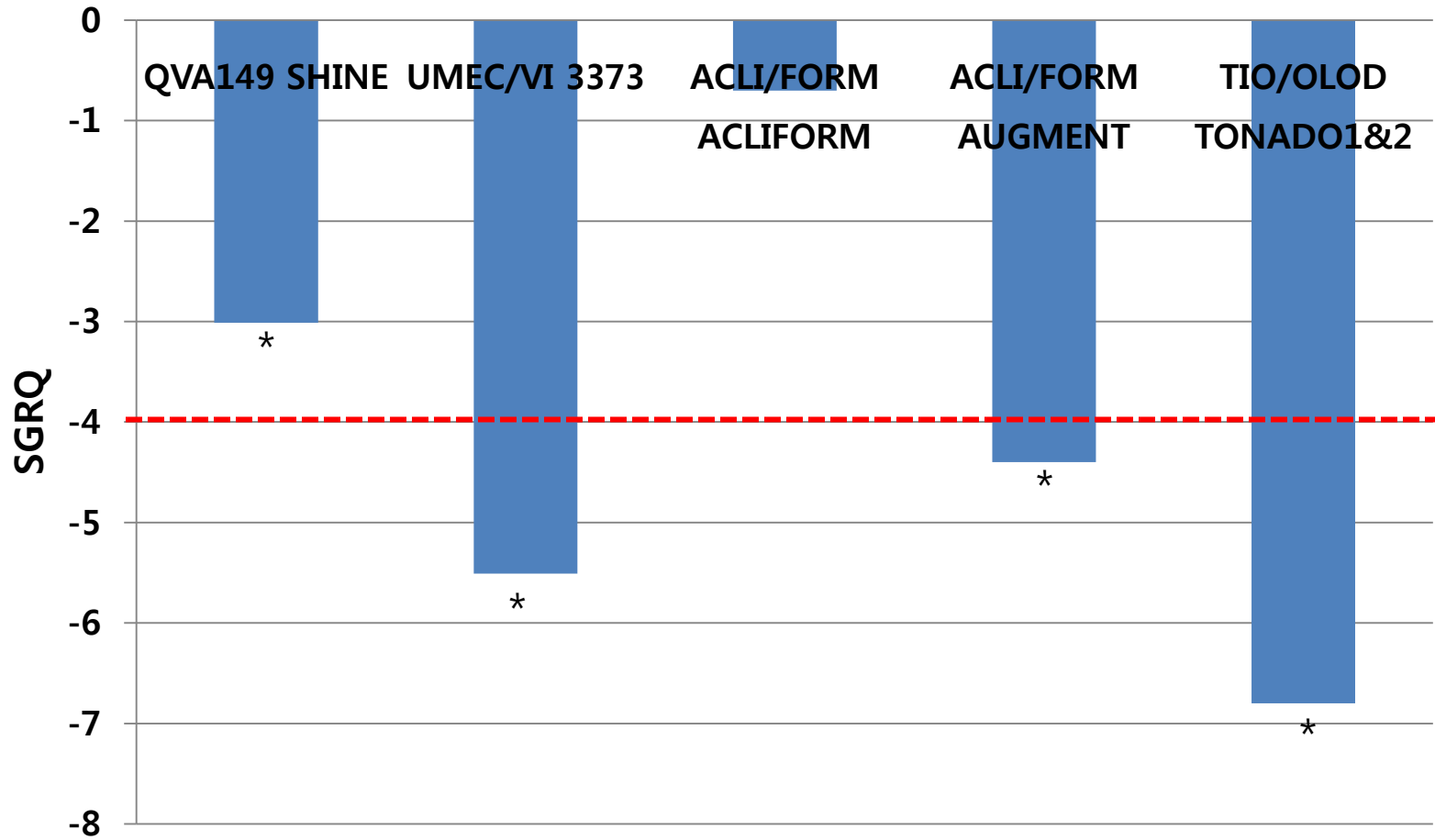
*p<0.001

LABA/LAMA FDC vs Monotherapy: TDI



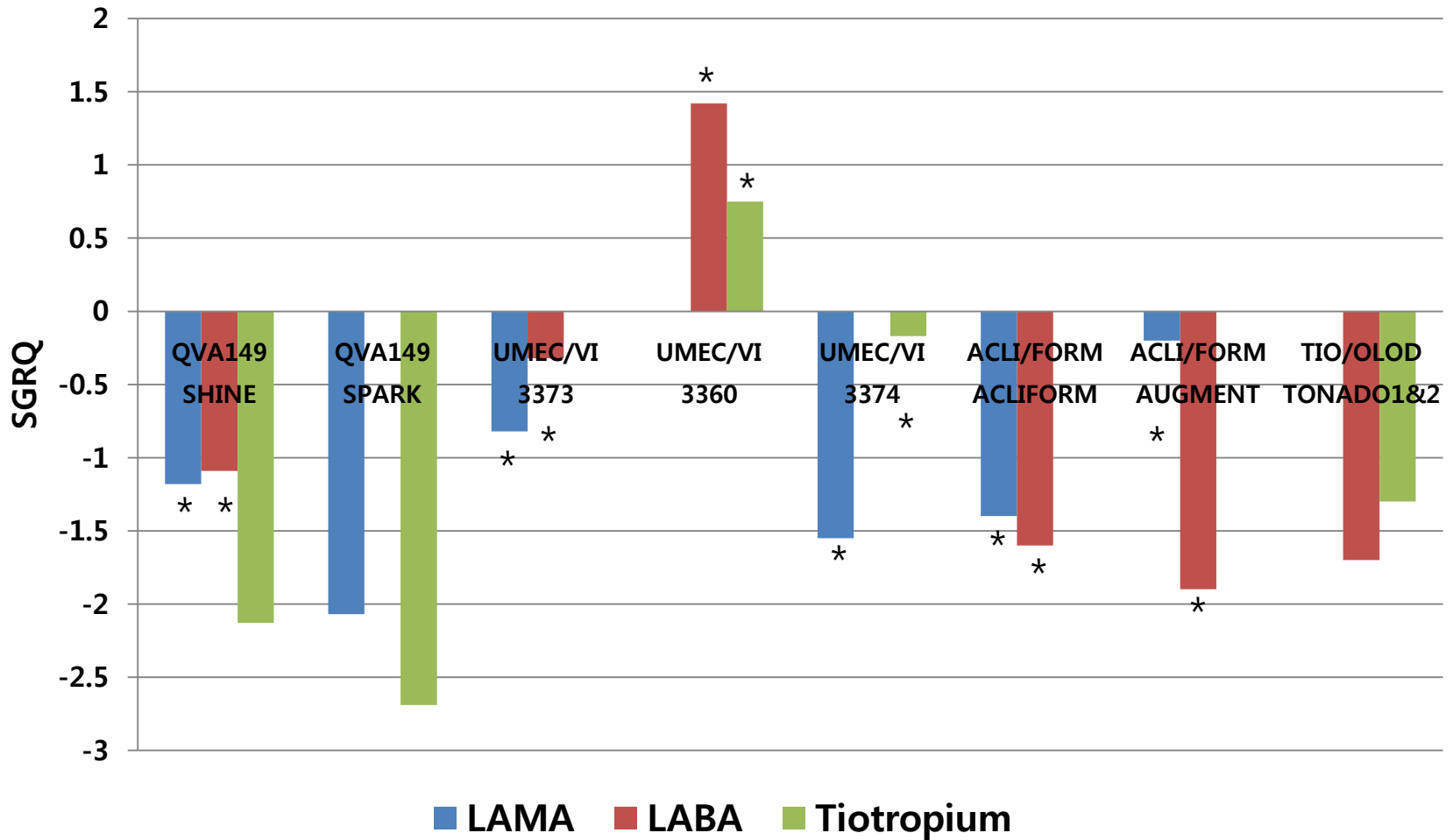
*Not statistically significant

LABA/LAMA FDC vs Placebo: SGRQ



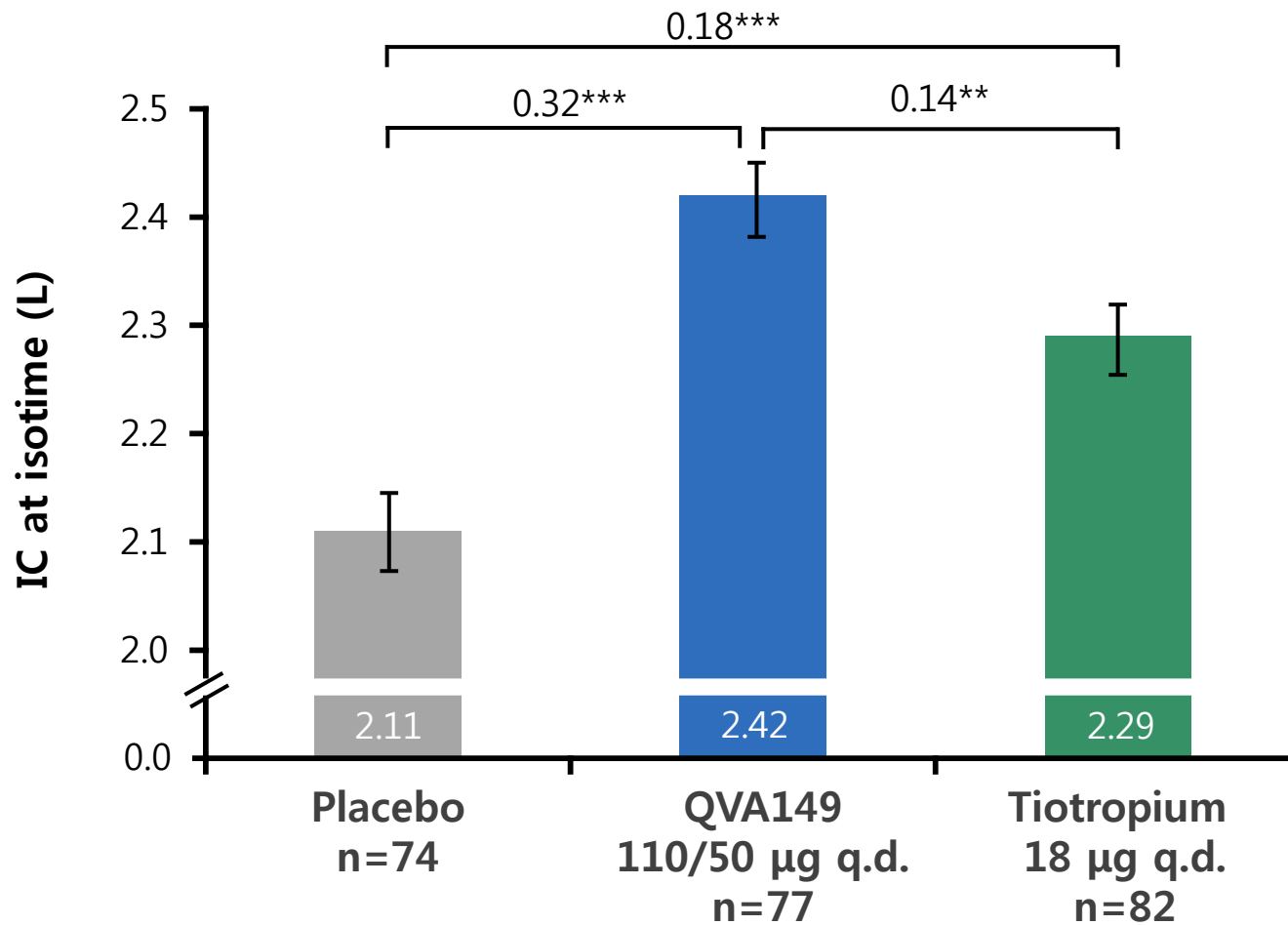
*p<0.001

LABA/LAMA FDC vs Monotherapy: SGRQ

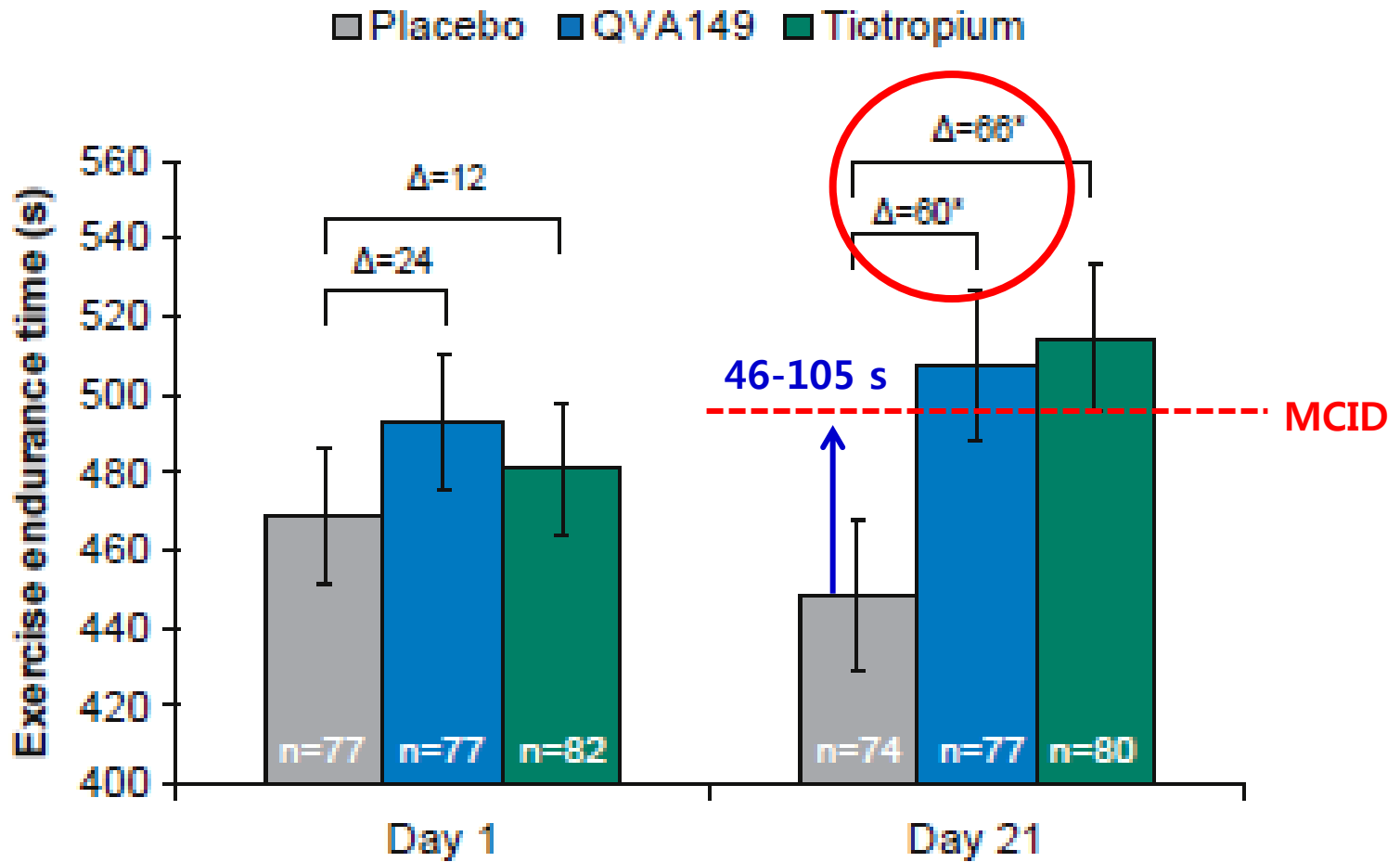


*Not statistically significant

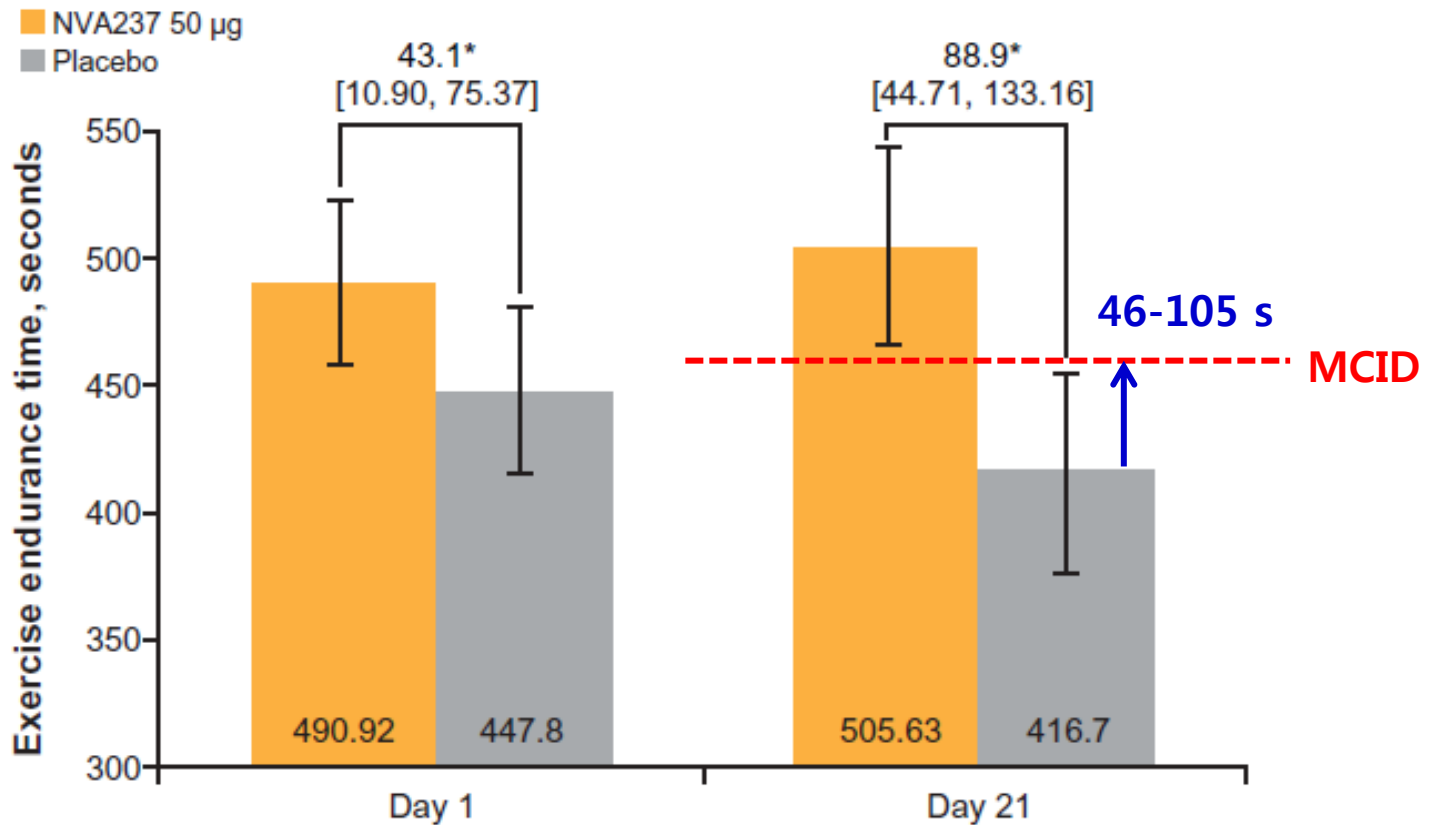
QVA149 (BRIGHT): Inspiratory Capacity



QVA149 (BRIGHT): Exercise endurance time

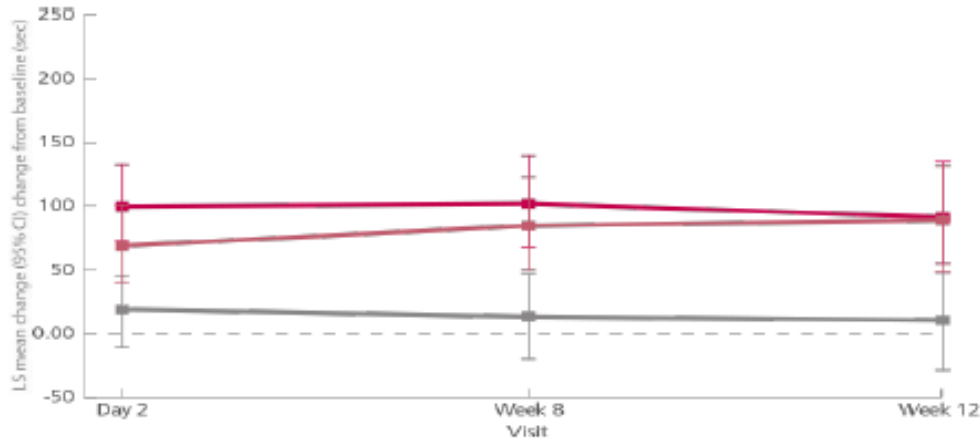


Glycopyrronium (GLOW3): Exercise endurance time



*P<0.001

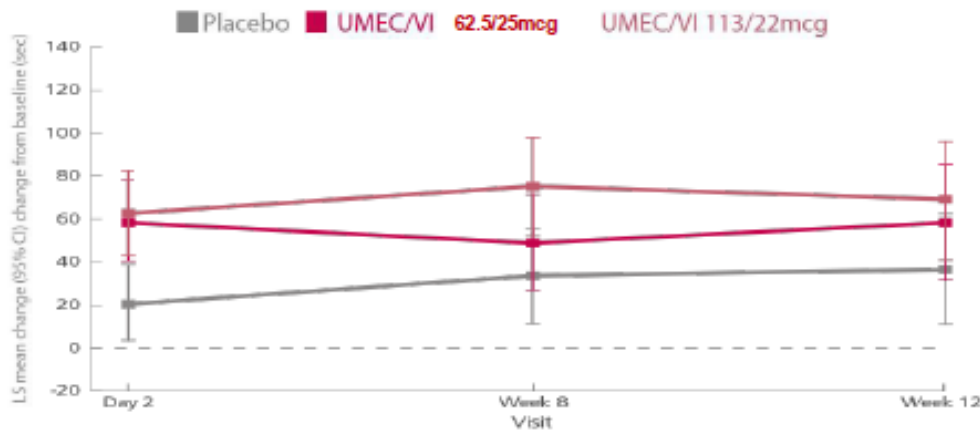
UMEC/VI (4417, 4418): Exercise endurance time



DB2114418

UMEC/VI 62.5/25mcg 69.4 sec ($p=0.003$) increase over placebo

69.4 s (MCID: 45-85 s)



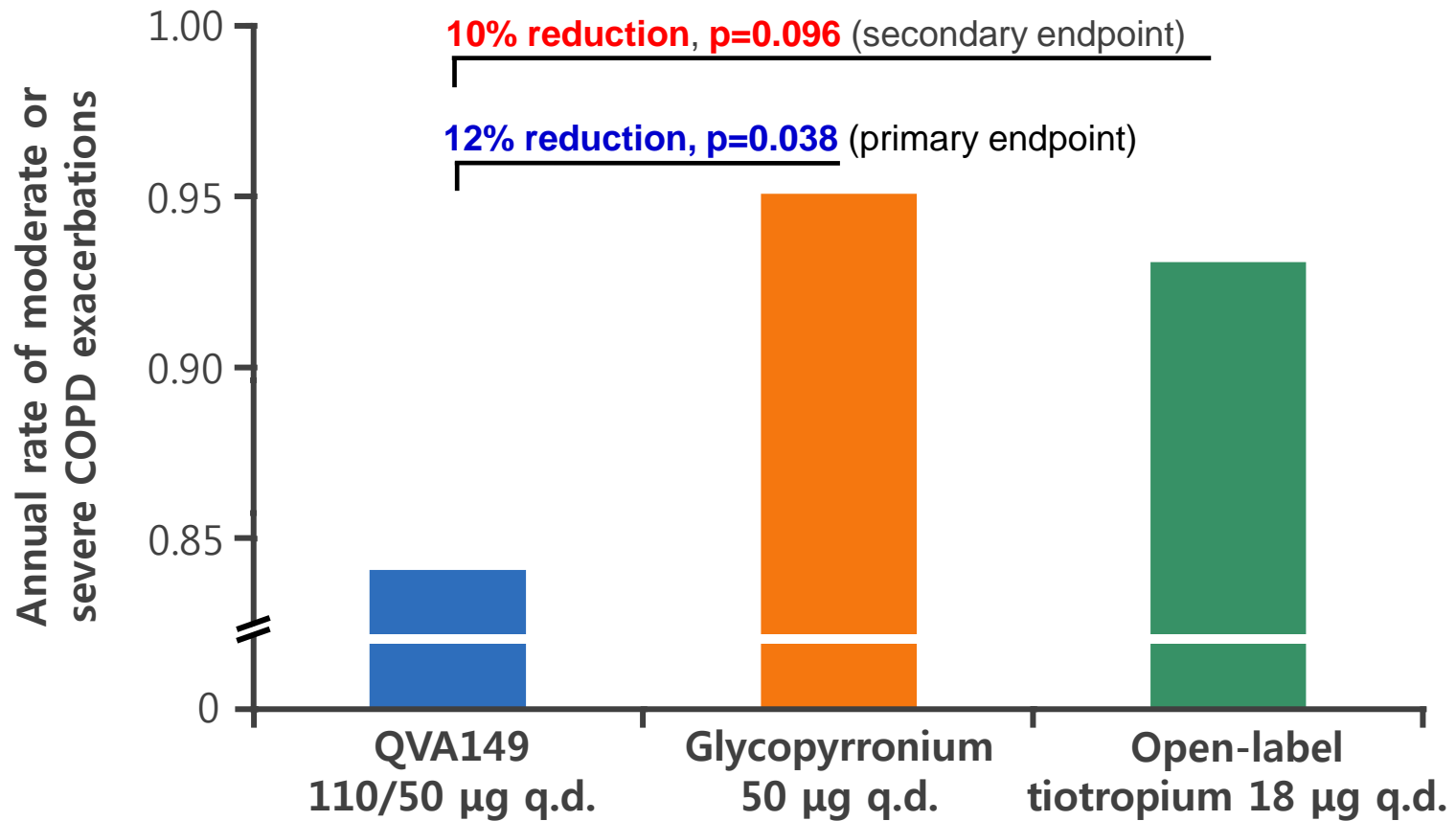
DB2114417

UMEC/VI 62.5/25mcg 21.9 sec ($p=NS$) change from placebo

21.9 s ($p=ns$)

While a valid estimation of the minimal important difference has yet to be established, a change in performance of 45-85 seconds is likely to be perceived by patients following treatment.¹

QVA149 (SPARK): Rate of moderate to severe COPD AE over 64 weeks



UMEC/VI (3360, 3374): Time to first exacerbation

| | Study 1 | | | | Study 2 | | | |
|---|-----------------------------|-----------------------------|--|---|-----------------------------|--------------------------------|--|---|
| | Tiotropium 18 µg (n=203) | Vilanterol 25 µg (n=205) | Umeclidinium 125 µg plus vilanterol 25 µg (n=208) | Umeclidinium 62.5 µg plus vilanterol 25 µg (n=207) | Tiotropium 18 µg (n=215) | Umeclidinium 125 µg (n=222) | Umeclidinium 125 µg plus vilanterol 25 µg (n=215) | Umeclidinium 62.5 µg plus vilanterol 25 µg (n=217) |
| Time to first on-treatment exacerbation (days) | | | | | | | | |
| HR (95% CI; p value) | | | | | | | | |
| Umeclidinium 125 µg plus vilanterol 25 µg vs monotherapy | 1.0 (0.4 to 2.3; p=1.00) | 0.6 (0.3 to 1.4; p=0.25) | .. | .. | 1.1 (0.6 to 2.3; p=0.71) | 0.6 (0.3 to 1.2; p=0.14) | .. | .. |
| Umeclidinium 62.5 µg plus vilanterol 25 µg vs monotherapy | 1.2 (0.5 to 2.6; p=0.71) | 0.7 (0.4 to 1.5; p=0.42) | .. | .. | 1.9 (1.0 to 3.6; p=0.06) | 1.0 (0.6 to 1.8; p=0.95) | .. | .. |

Are these findings clinically relevant?

- Effect of dual bronchodilatation in FEV₁:
not synergetic, less than additive
- Improvement in FEV₁:
not necessarily translate into any meaningful differences in patient-based outcomes
- a dual bronchodilators provides marginal clinical benefits?
- using MCIDs or responder analysis to assess clinical efficacy?

Evidence summary: new medicine

Chronic obstructive pulmonary disease: umeclidinium/vilanterol combination inhaler (Anoro Ellipta)

Published: 06 November 2014

Key points from the evidence

Summary

combination inhaler. However, the clinical relevance of these benefits is unclear. There is limited evidence on patient-orientated outcomes such as shortness of breath, quality of life outcomes or exacerbation rates.

COPD. The combination inhaler has been compared in randomised controlled trials (RCTs) with its individual components, tiotropium monotherapy and placebo. Studies suggest that there are benefits for forced expired volume in 1 second (FEV₁) with the umeclidinium/vilanterol combination inhaler. However, the clinical relevance of these benefits is unclear. There is limited evidence on patient-orientated outcomes such as shortness of breath, quality of life outcomes or exacerbation rates.

QVA149: Safety data

| Title | Patients (n) | Total AEs | AEs leading to discontinuation of study | Total SAEs | Deaths | CCV AEs | CCV SAEs | MACE (total) | Atrial Fibrillation/flutter events |
|------------------------------|--------------|------------|---|------------|---------|----------|----------|--------------|------------------------------------|
| QVA149 110/50 µg q.d. | 1076 | 593 (55.1) | 37 (3.4) | 59 (5.5) | 3 (0.3) | 19 (1.8) | 6 (0.6) | 3 (0.3) | 9 (0.8) |
| Placebo | 345 | NR | NR | NR | NR | 9 (2.6) | 1 (0.3) | 0 | NR |
| Indacaterol 150 µg q.d. | 476 | 291 (61.1) | 24 (5.0) | 26 (5.5) | 2 (0.4) | 12 (2.5) | 4 (0.8) | 2 (0.4) | 7 (1.5) |
| Glycopyrronium 50 µg q.d. | 473 | 290 (61.3) | 14 (3.0) | 29 (6.1) | 1 (0.2) | 14 (3.0) | 6 (1.3) | 3 (0.6) | 10 (2.1) |
| Tiotropium 18 µg q.d. | 519 | 295 (56.8) | 10 (1.9) | 20 (3.9) | 3 (0.6) | 9 (1.7) | 3 (0.6) | 3 (0.6) | 7 (1.3) |
| SFC 50/500 µg b.i.d. | 264 | 159 (60.2) | 27 (10.2) | 14 (5.3) | 1 (0.4) | 6 (2.3) | 3 (1.1) | 1 (0.4) | 7 (2.7) |

*Pooled 6-month safety data from SHINE, ILLUMINATE, ENLIGHTEN and ARISE studies

UMEC/VI (3360,3374): Safety data

| | Study 1 | | | | Study 2 | | | |
|--|--------------------------|--------------------------|---|--|--------------------------|-----------------------------|---|--|
| | Tiotropium 18 µg (n=208) | Vilanterol 25 µg (n=209) | Umeclidinium 125 µg plus vilanterol 25 µg (n=214) | Umeclidinium 62.5 µg plus vilanterol 25 µg (n=212) | Tiotropium 18 µg (n=215) | Umeclidinium 125 µg (n=222) | Umeclidinium 125 µg plus vilanterol 25 µg (n=215) | Umeclidinium 62.5 µg plus vilanterol 25 µg (n=217) |
| On-treatment adverse events | 82 (39%) | 99 (47%) | 94 (44%) | 108 (51%) | 126 (59%) | 131 (59%) | 133 (62%) | 127 (59%) |
| Post-treatment adverse events | 2 (<1%) | 3 (1%) | 5 (2%) | 6 (3%) | 3 (1%) | 2 (<1%) | 8 (4%) | 3 (1%) |
| Drug-related adverse events | 7 (3%) | 12 (6%) | 9 (4%) | 11 (5%) | 16 (7%) | 28 (13%) | 17 (8%) | 16 (7%) |
| Adverse events that led to discontinuation of study drug or withdrawal from study* | 9 (4%) | 10 (5%) | 15 (7%) | 10 (5%) | 11 (5%) | 17 (8%) | 15 (7%) | 20 (9%) |
| On-treatment serious adverse events | 13 (6%) | 15 (7%) | 5 (2%) | 7 (3%) | 9 (4%) | 15 (7%) | 15 (7%) | 22 (10%) |
| Post-treatment serious adverse events | 0 | 1 (<1%) | 2 (<1%) | 2 (<1%) | 0 | 1 (<1%) | 2 (<1%) | 1 (<1%) |
| On-treatment or post-treatment fatal adverse events | 0 | 1 (<1%) | 0 | 1 (<1%) | 2 (<1%) | 0 | 1 (<1%) | 1 (<1%) |

LABA/LAMA FDC: Study durations

| Drug | Study | Weeks | Drug | Study | Weeks | Drug | Study | Weeks |
|--------|------------|-------|---------|-----------|-------|----------|----------|-------|
| QVA149 | SHINE | 26 | UMEC/VI | 3373 | 24 | ACLI/FOM | ACLIFORM | 24 |
| | SPARK | 64 | | 3360 | 24 | | AUGMENT | 24 |
| | ILLUMINATE | 64 | | 3374 | 24 | | | |
| | ENLIGHT | 52 | | ZEP117115 | 24 | TIO/OLOD | TONADO1 | 52 |
| | ARISE | 52 | | 4417 | 12 | | TONAOD2 | 52 |
| | LANTERN | 26 | | 4418 | 12 | | | |
| | BRIGHT | 3 | | | | | | |
| | BLAZE | 6 | | | | | | |
| | BEACON | 4 | | | | | | |

Clinical trials for 6-12 months

→ Long-term studies are required to explore the efficacy & safety



Optimization vs Maximization

Manage Stable COPD: Goals of Therapy

- **Relieve symptoms**
- **Improve exercise tolerance**
- **Improve health status**



**Reduce
Symptoms**

- **Prevent disease progression**
- **Prevent and treat exacerbations**
- **Reduce mortality**



**Reduce
Risk**

Monotherapy vs a dual bronchodilator

- **Relieve symptoms**
- **Improve exercise tolerance**
- **Improve health status**

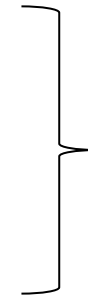
**Reduce
Symptoms?**

- **Prevent disease progression**
- **Prevent and treat exacerbations**
- **Reduce mortality**

??

Monotherapy vs a dual bronchodilator

- Relieve symptoms
- Improve exercise tolerance
- Improve health status



| Mono | Dual |
|------|------|
| ○ | △ |
| ○ | △ |
| ○ | △ |

- Prevent disease progression
- Prevent and treat exacerbations
- Reduce mortality

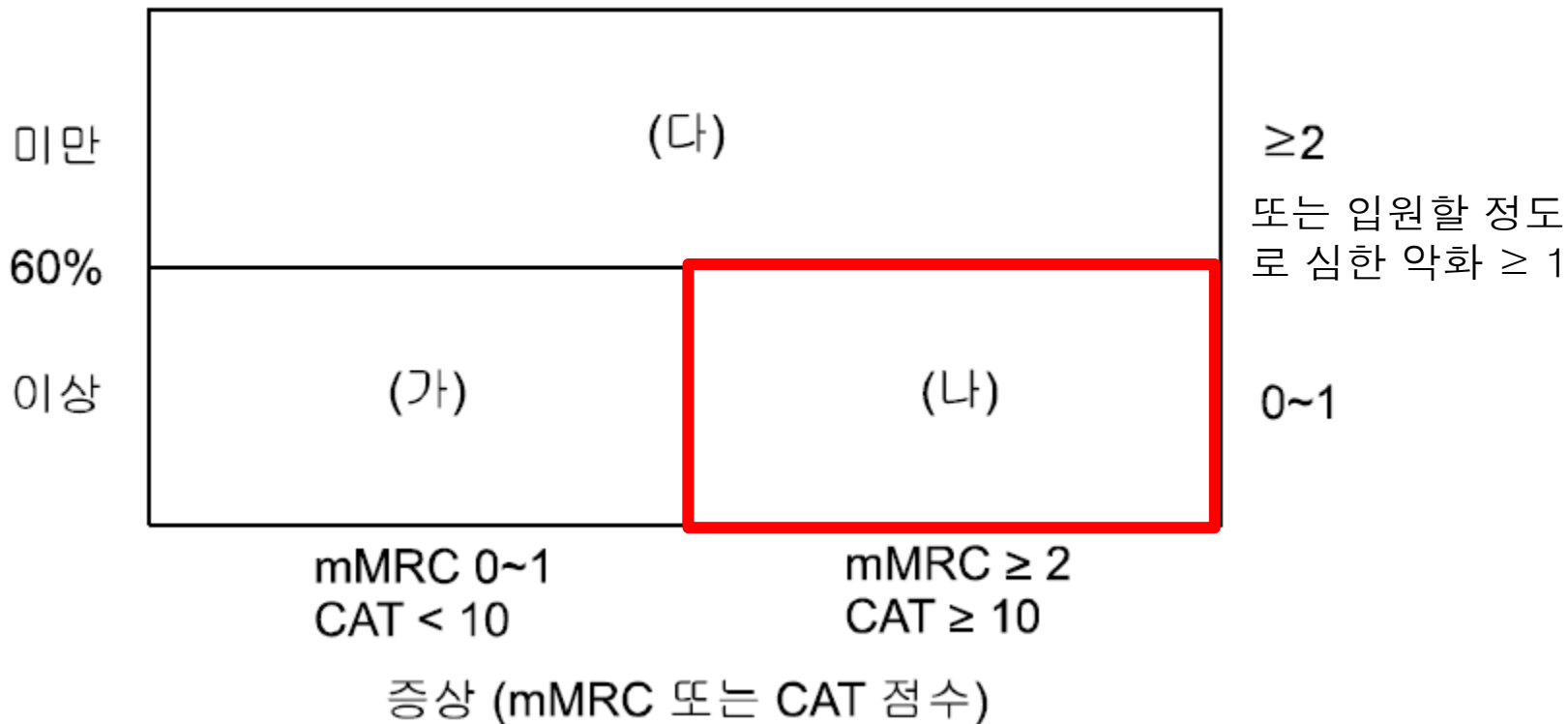


| Mono | Dual |
|------|------|
| △ | ? |
| ○ | △ |
| ? | ? |

Optimization vs Maximization

FEV1 (% 정상예측치)

지난해 악화횟수



Recommendation

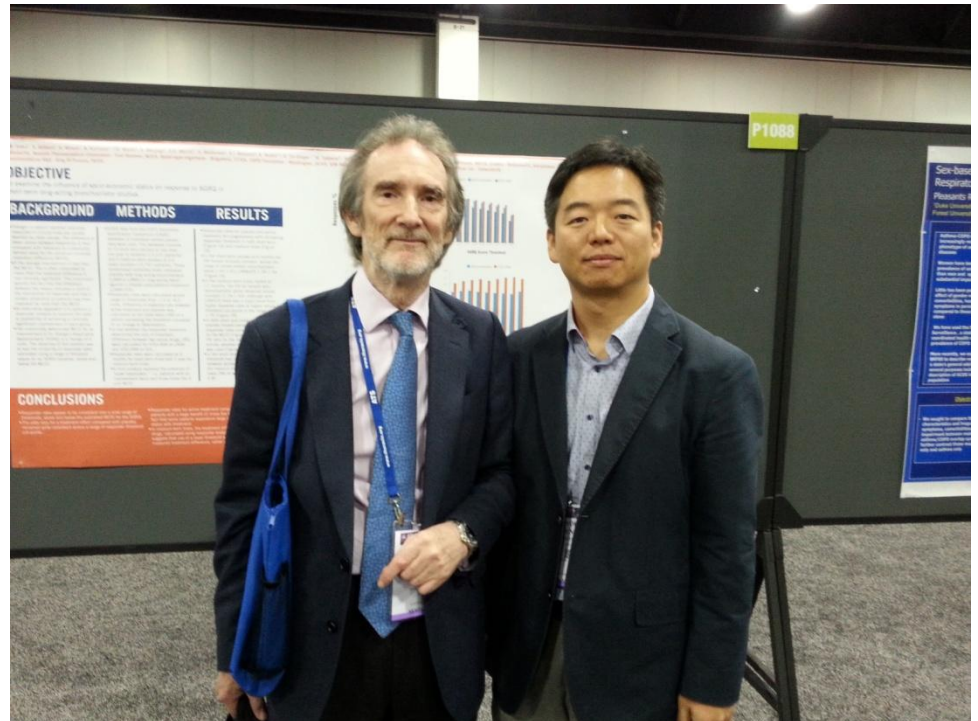
- **Monotherapy** should be the first choice for maintenance treatment in stable COPD
- **A dual bronchodilator** should be recommended in patients who remain breathless or symptomatic

Summary

- **Increasing number of drugs for COPD**
 - : increases the number of therapeutic options**
 - : makes the choice more complicated**
- **Further data on the efficacy and safety of a dual bronchodilators are required before changes in treatment recommendations can be considered**
 - : hospitalization, exacerbation, mortality...**
- **Further studies should be designed to give necessary evidence to the optimal sequence of monotherapy and a dual bronchodilators**

Acknowledgement

- GSK
- Novartis
- Dr. Paul Jones





Thank you for your attention