Ultra LABAs in COPD

Puneet Saxena

Changing the Natural History

- Smoking cessation
- LTOT
- LVRS in selected patients

- Pharmacotherapy?

•*Anthonisen NR. The lung health study. JAMA. 1994*
•*Nocturnal Oxygen Therapy Group, et al. Ann Intern Med. 1980*
•*Naunheim KS. Ann Thorac Surg. 2006*

Effect of Pharmacotherapy on Rate of Decline of Lung Function in Chronic Obstructive Pulmonary Disease

Results from the TORCH Study

- Post hoc analysis of the TORCH study
- Effects of
  - combined salmeterol 50 µg plus fluticasone propionate 500 µg
  - either component alone
  - Placebo
- On the rate of post-bronchodilator FEV1 decline in patients with moderate or severe COPD
- 5,343 patients were studied

Celli BR et al. Am J Respir Crit Care Med. 2008

Adjusted yearly rate of decline in FEV1 by treatment group

	Placebo (n = 1,261)	SAL (n = 1,334)	FP (n = 1,356)	SFC (n = 1,392)
Adjusted rate of decline (SE), ml/yr	−55.3 (3.2)	−42.3 (3.1)	−42.3 (3.1)	−39.0 (3.0)
Active treatment minus placebo (SE), ml/yr	–	13.0 (4.4)	13.0 (4.4)	16.3 (4.4)
95% CI	–	4.3, 21.7	4.3, 21.7	7.7, 24.9
P value	–	0.003	0.003	< 0.001
SFC minus components (SE), ml/yr	–	3.3 (4.3)	3.3 (4.3)	–
95% CI	–	−5.1, 11.7	−5.1, 11.6	–
P value	–	0.441	0.445	–

	Placebo (n = 1,261)	SAL (n = 1,334)	FP (n = 1,356)	SFC (n = 1,392)
Adjusted rate of decline (SE), %/yr	−1.5 (0.1)	−1.0 (0.1)	−1.1 (0.1)	−0.9 (0.1)
Active treatment minus placebo (SE), %/yr	–	0.5 (0.2)	0.4 (0.2)	0.6 (0.2)
95% CI	–	0.2, 0.8	0.1, 0.8	0.3, 0.9
P value	–	0.002	0.006	< 0.001
SFC minus components (SE),%/yr	–	0.1 (0.2)	0.1 (0.2)	–
95% CI	–	−0.2, 0.4	−0.2, 0.4	–
P value	–	0.627	0.401	–

Celli BR et al. Am J Respir Crit Care Med. 2008

Search for the ‘Holy Grail’

- Ideal Bronchodilator
  - Long acting
  - Instant action
  - Minimal side effects

- LABA
- LAMA
- Ultra-LABA

Need for Ultra LABAs

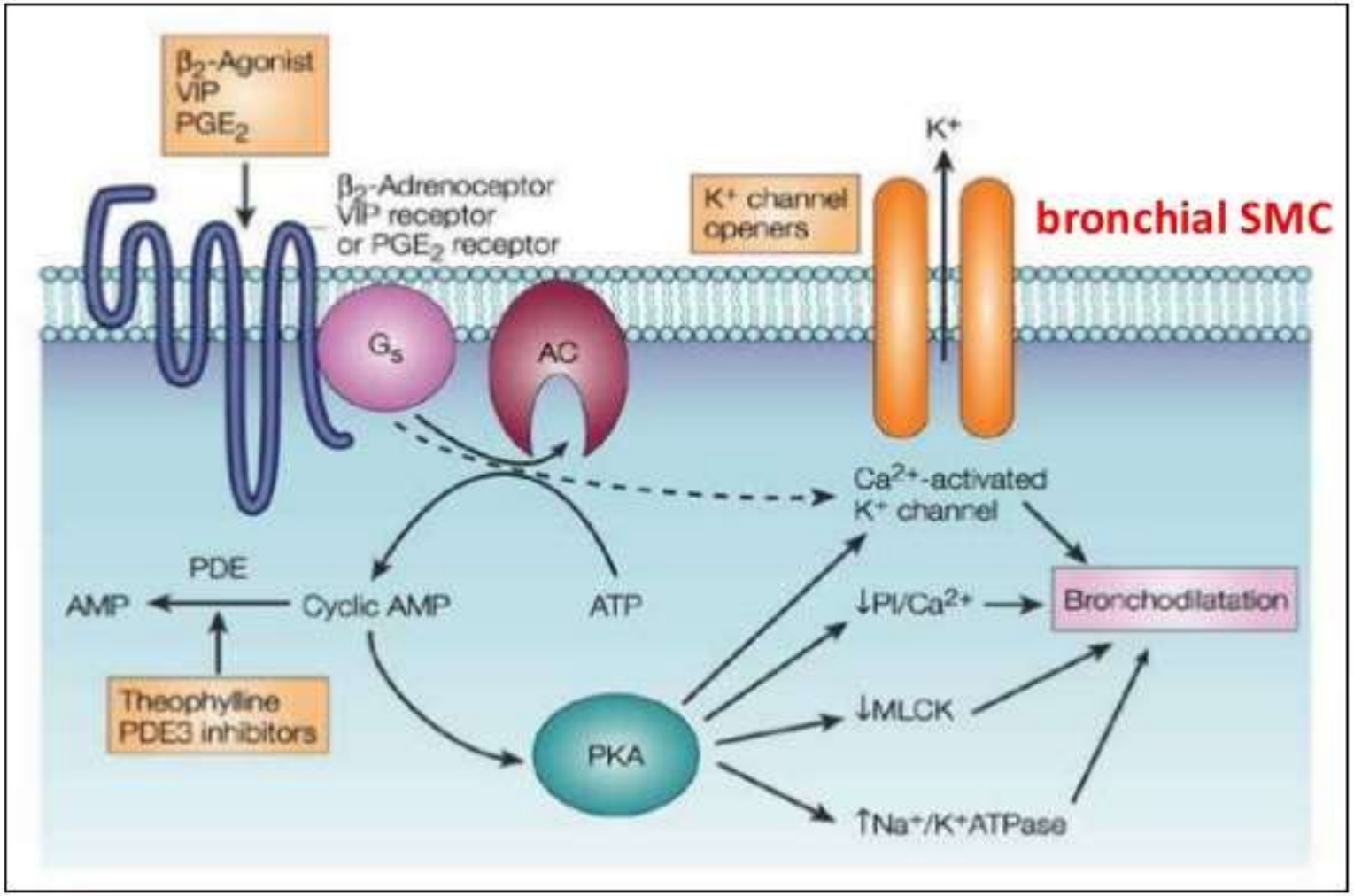
- Importance of once daily dosing
  - Noncompliance – increased morbidity in COPD
- Potency
  - binding ability and local concentration
- Onset of action
  - water solubility of the molecule
- Better β2:β1 profile

Treatment of COPD: Relationships between daily dosing frequency, adherence, resource use, and costs

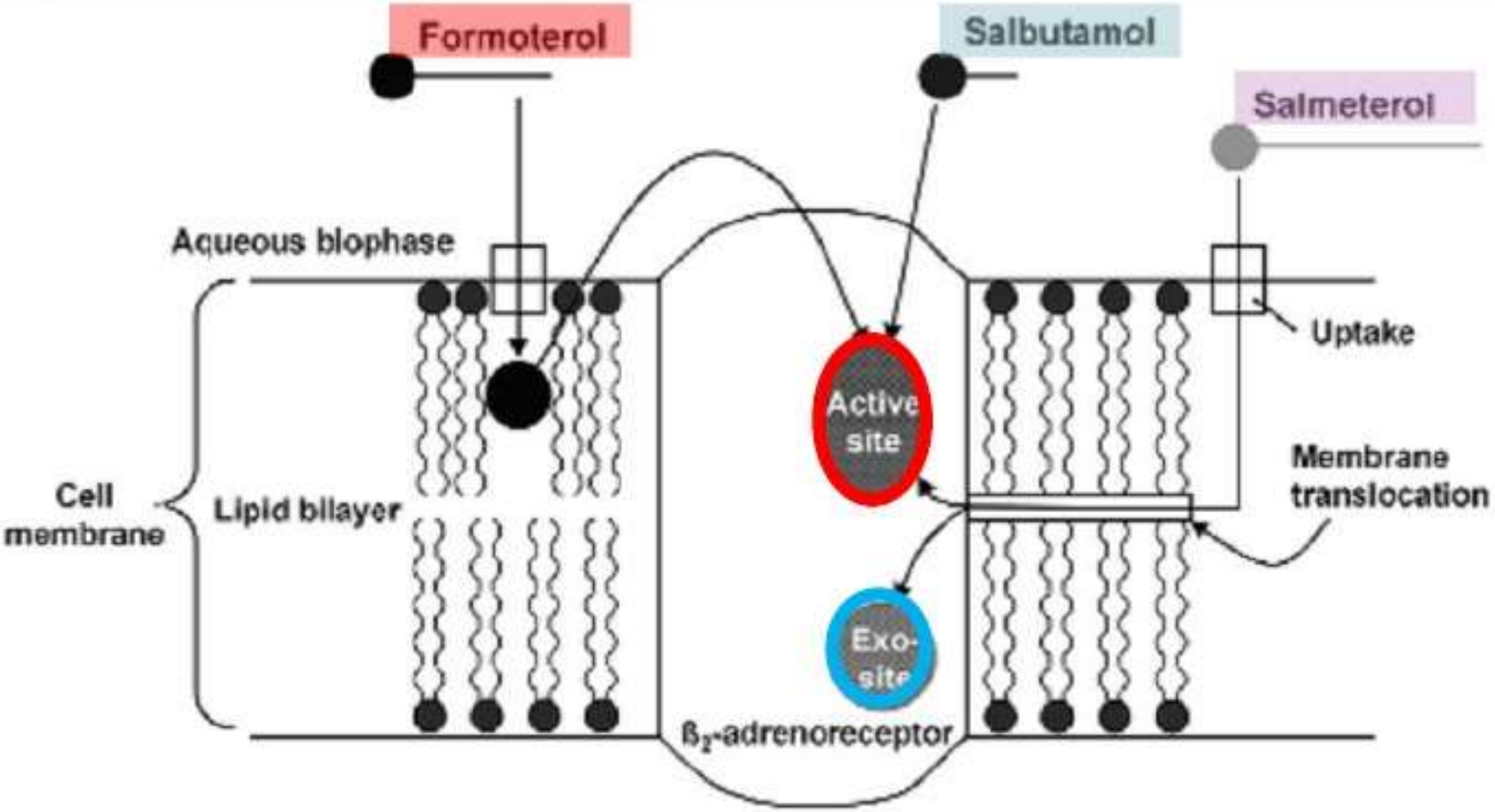
- Retrospective study - 55,076 COPD patients
- Adherence was strongly correlated with dosing frequency
- PDC was 43.3%, 37.0%, 30.2% and 23.0% for QD, BID, TID, and QID patient cohorts
- Adherence was correlated with healthcare resource utilization
- For 1000 COPD patients, a 5% point increase in PDC reduced the annual number of inpatient visits (2.5%) and emergency room visits (1.8%)

Toy EL et al. Respir Med. 2011

Scientific rationale



Mechanism of action



Johnson M. Paediatric respiratory reviews 2001;2:57-62.

Approved Ultra-LABAs

- Indacaterol:
  - approved by the EMA on Nov 30, 2009 and by Russian FDA-equivalent under the trade name Onbrez Breezhaler
  - United States - approved by the FDA under the trade name Arcapta Neohaler on July 1, 2011
- Olodaterol:
  - approved in some EU countries and Russia, and by the US FDA on July 31, 2014 (Striverdi Respimat)
- Vilanterol : available only as a component of combination drugs:
  - with fluticasone furoate: Breo Ellipta (U.S.), Relvar Ellipta (EU, RU)- approved by the FDA on May 2013 as once-daily inhaled therapy for COPD
  - with umeclidinium bromide: Anoro Ellipta
    - FDA -December 18, 2013
    - EU and RU- March 28, 2014

Under development

- Abediterol (codenamed LAS100977)
- Salmefamol [salbutamol and para-methoxyamphetamine (PMA) hybrid]

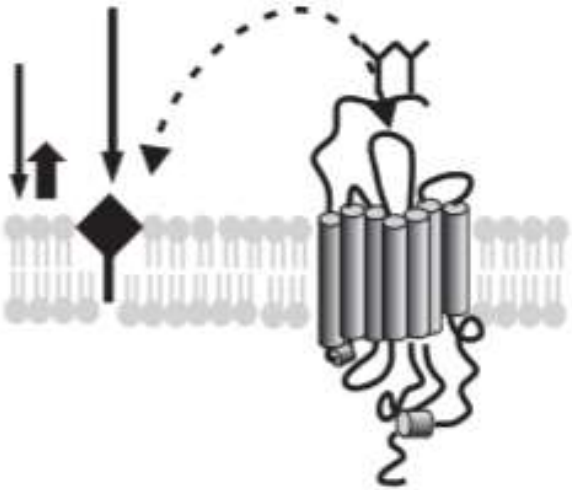
Failed agents

- Carmoterol (formerly TA-2005)
- Milveterol
- PF-610355
- AZD-3199

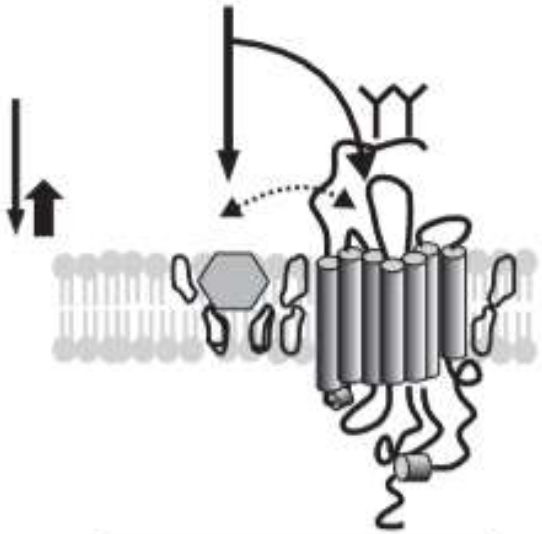
Indacaterol

- Chirally pure inhaled ultra-LABA
- Significant β2-adrenoceptor potency, a fast onset of action, and sustained duration of action
- Nearly a full agonist
  - 73% effect compared to the full in-vitro agonist isoprenaline (salmeterol 38%)
- Onset of action 30 ± 4 min
- Duration – 24h
- β2 :β1 similar to formoterol
- Greater cardiovascular safety margin than formoterol or salmeterol

Sturton RG et al. J Pharmacol Exp Ther. 2008;324:70–75



Aqueous biphase



Salmeterol

- Lipophilic (fat soluble)
- Retained in lipid membrane
- Slow release from cell membrane
- 12 hours duration of action

Indacaterol

- Lipophilic (fat soluble)
- Retained in raft domain of lipid membrane
- Ultra slow release from cell membrane
- 24 hours duration of action

Cazzola M, et al. Drugs Today (Barc). 2010;46:139–150

Indacaterol – clinical studies

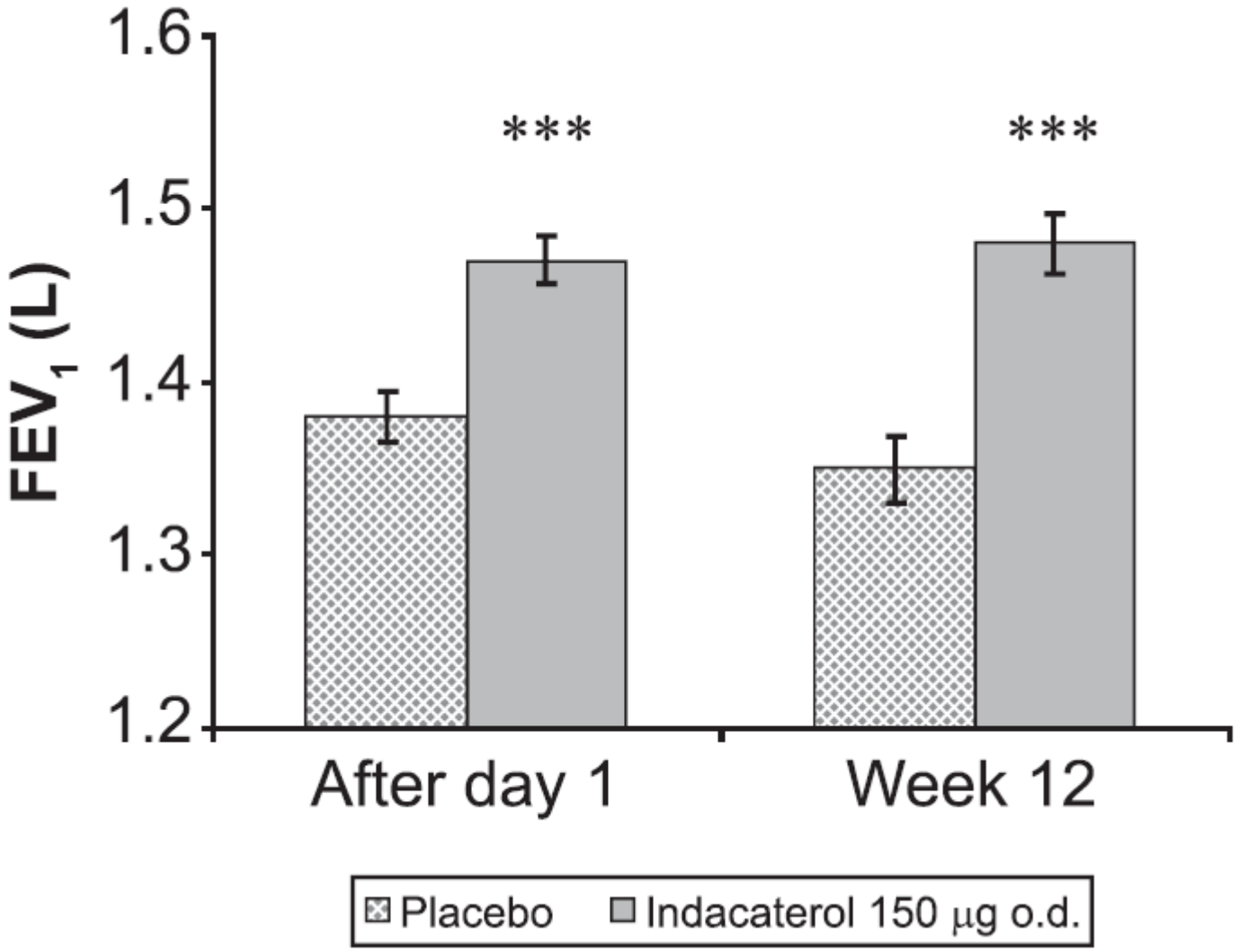
Study	Study design	N	Treatment	Outcomes
Bauwens et al.	Randomized, double-blind, placebo-controlled, crossover	51	Indacaterol 150, 300 or 600 µg o.d., placebo o.d. or formoterol (12 µg b.i.d.)	24-h trough FEV1 significantly higher for all doses of indacaterol vs. placebo and for 300 and 600 µg vs. formoterol
LaForce et al.	Randomized, three- period crossover study (14-day treatment periods with 14-day washouts between treatments)	68	Indacaterol 300 µg or placebo o.d. and salmeterol 50 µg b.i.d. for 14 days	Trough FEV1 for indacaterol 200 mL higher than placebo and 90 mL higher than salmeterol.
Rennard et al.	Randomized, double-blind, placebo-controlled dose-ranging trial of indacaterol followed by a tiotropium open-label extension period	635	Indacaterol 50, 100, 200 or 400 µg or placebo o.d. via MDDPI, indacaterol 400 µg q.d. via SDDPI for 7 days, tiotropium 18 µg o.d. (open-label) via a SDDPI	Clinically relevant improvements in FEV1 AUC 22-24h vs. placebo for 400 and 200 µg doses on day 1 and all doses on day 7. Increase in FEV1 from 5 min to 24 h post-dose for all indacaterol doses. Effects of indacaterol on FEV1 were similar to those of tiotropium.

Efficacy and safety of indacaterol 150 μg once-daily in COPD: a double-blind, randomised, 12-week study

INLIGHT 1

- Randomized, double-blind, placebo-controlled
- 416 patents
- Efficacy variables
  - 24-h trough FEV1 (mean of 23 h 10 min and 23 h 45 min post-dose) at Week 12 (primary endpoint) and after Day 1
  - Percentage of COPD days with poor control
- Safety variables
  - Adverse events
  - Mean serum potassium
  - Blood glucose
  - QTc
  - Vital signs

Feldman G et al. BMC Pulm Med. 2010 Mar 8;10:11



- Reduced the % of days of poor control by 22.5% ($p < 0.001$)
- Reduced use of rescue medication ($p < 0.001$)
- No difference in adverse effect profile

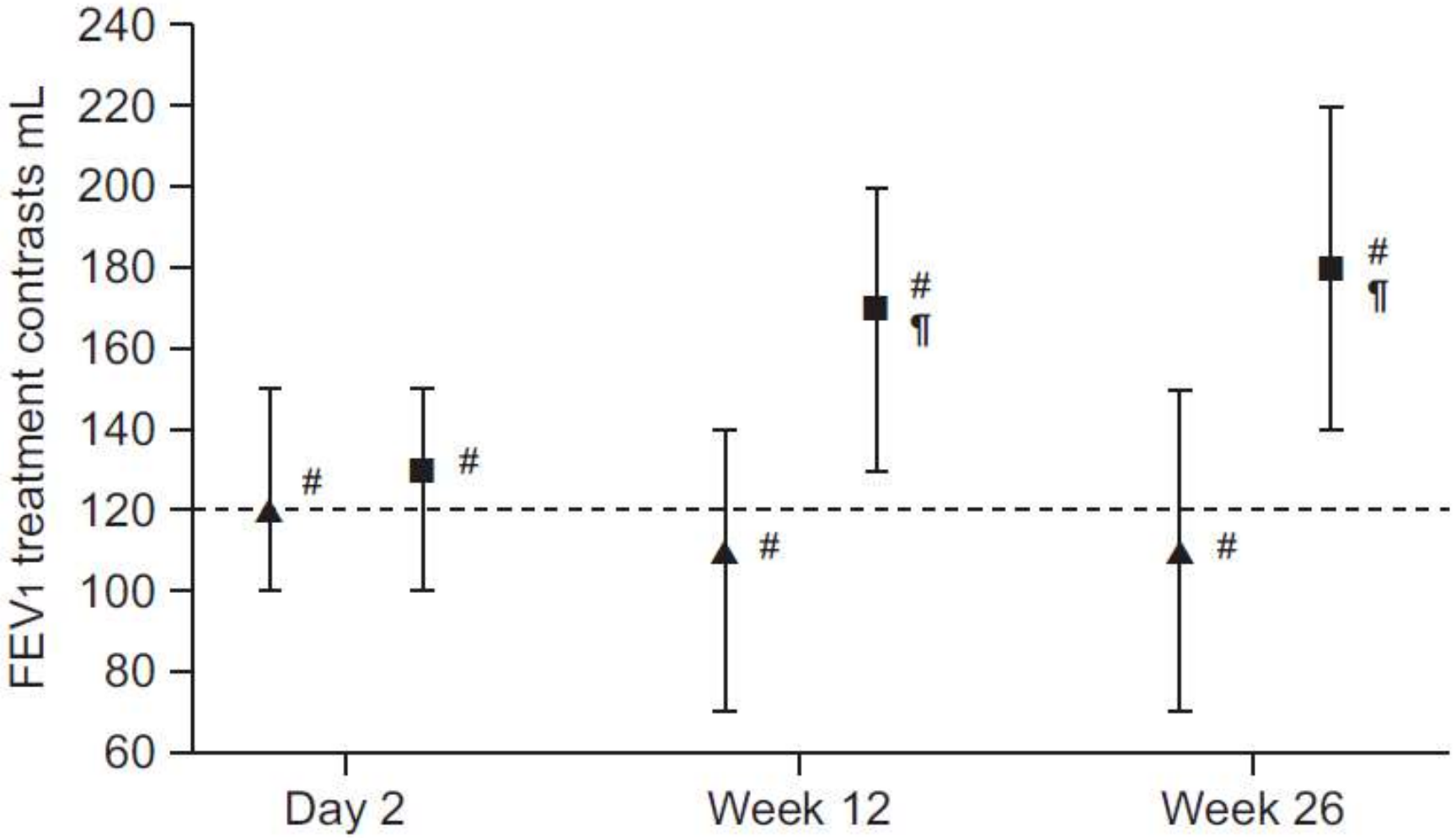
Feldman G et al. BMC Pulm Med. 2010 Mar 8;10:11

Once-daily indacaterol *versus* twice-daily salmeterol for COPD: a placebo-controlled comparison

INLIGHT-2

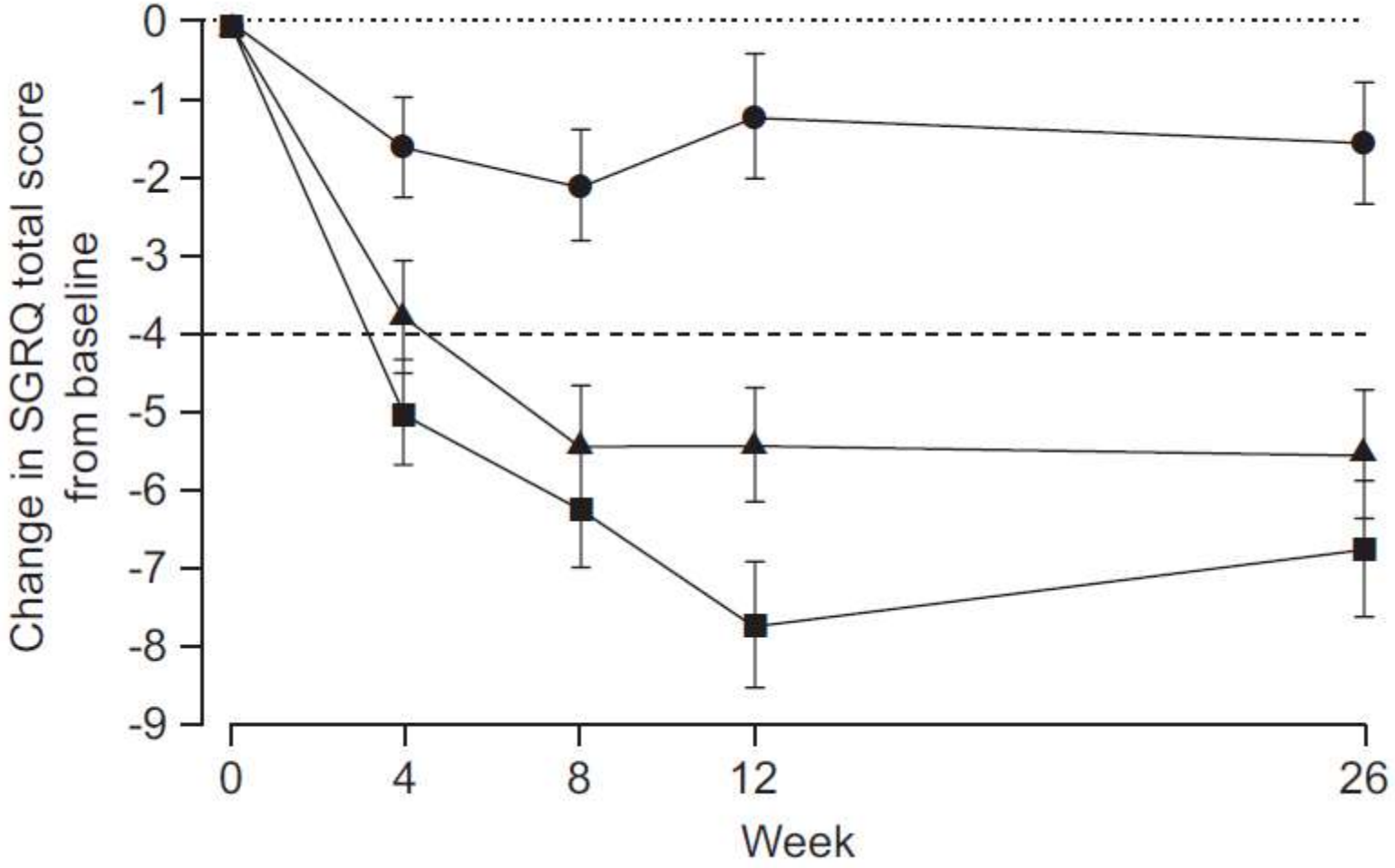
- Double-blind, RCT
- 1,002 patients; 838 (84%) completed the study
- Moderate-to-severe COPD
- 6 m treatment with indacaterol (150 µg OD), salmeterol (50 µg BD) or placebo
- Primary efficacy end-point – trough FEV1 after 12 weeks.

Kornmann O. Eur Respir J 2011; 37: 273–279



- Also translated to better COPD control and less use of rescue inhalers

Kornmann O. Eur Respir J 2011; 37: 273–279



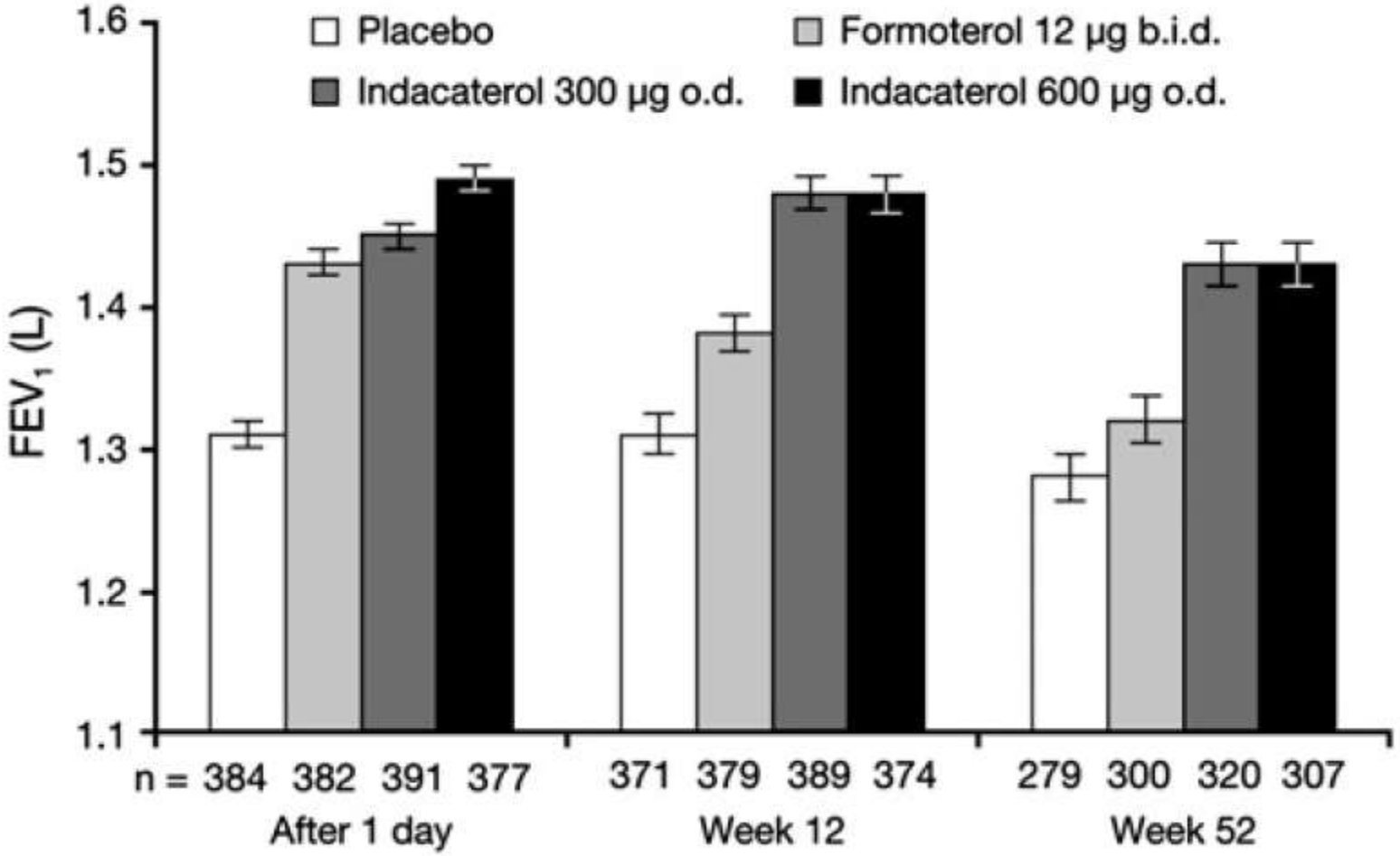
- Similar trends in TDI

Kornmann O. Eur Respir J 2011; 37: 273–279

Indacaterol vs Formoterol

- INVOLVE Study
- Double-blind, double-dummy RCT – 52 wks
- Moderate to severe COPD
  - Indacaterol 300 µg OD (n=437)
  - Indacaterol 600 µg OD (n=428)
  - Formoterol 12 µg (n=435)
  - Placebo (n=432)
- Primary efficacy variable – trough FEV1 after 12 weeks

Dahl R et al. Thorax 2010;65:473e479.



- Indacaterol increased 24 h postdose FEV1 after 12 weeks by 170 ml (both doses) versus placebo and by 100 ml versus formoterol (all $p<0.001$)
- Differences were maintained at 52 weeks
- Indacaterol was more effective than formoterol in improving TDI score and reducing the need for as-needed salbutamol
- Safety profile similar
- No difference – HRQoL, COPD control, Exacerbation rates

Dahl R et al. Thorax 2010;65:473e479.

Cochrane Library

Cochrane Database of Systematic Reviews

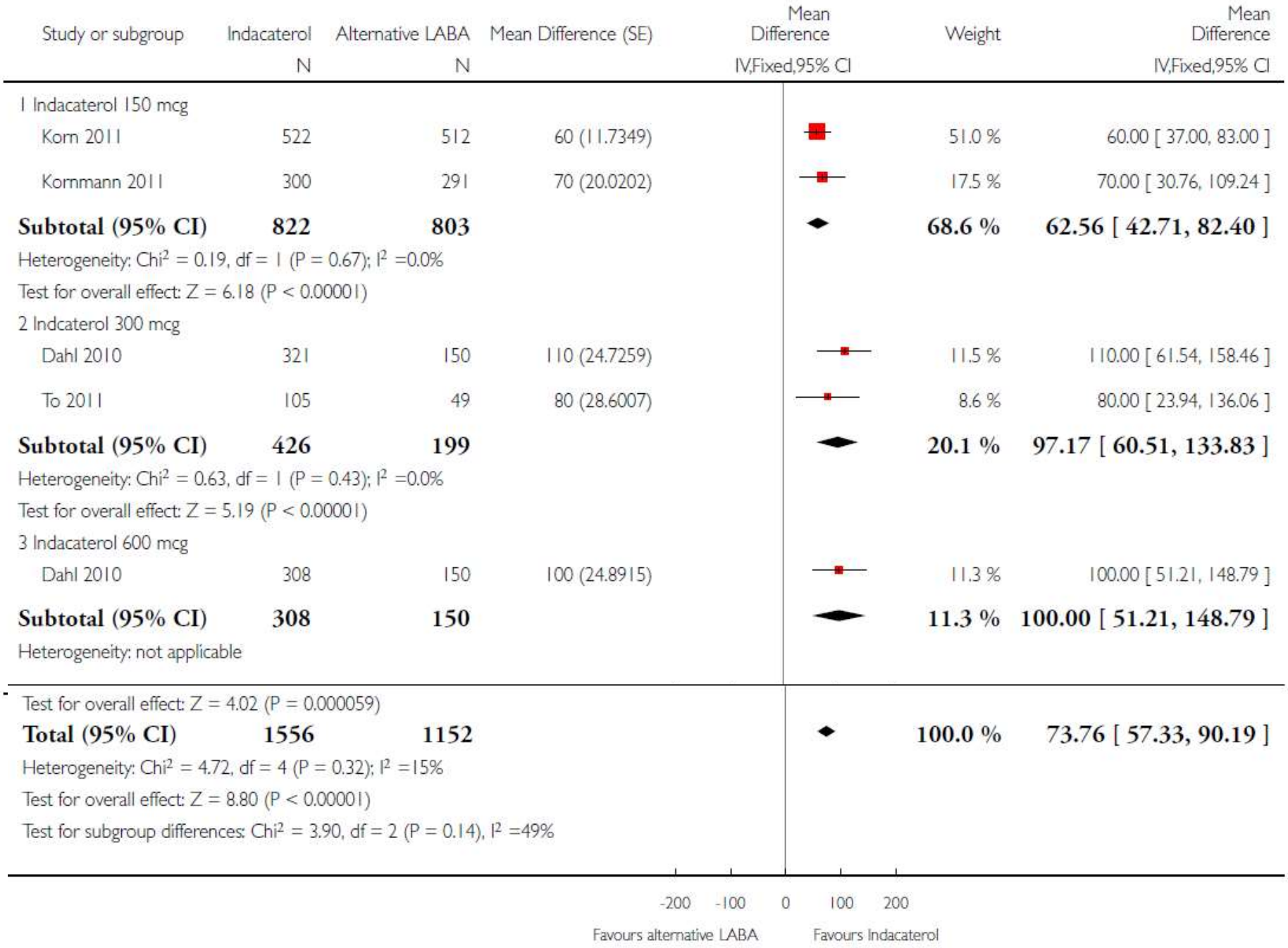
Indacaterol, a once-daily beta$_2$-agonist, versus twice-daily beta$_2$-agonists or placebo for chronic obstructive pulmonary disease (Review)

Geake JB et al. Cochrane Database of Systematic Reviews 2015, Issue 1. Art. No.: CD010139.

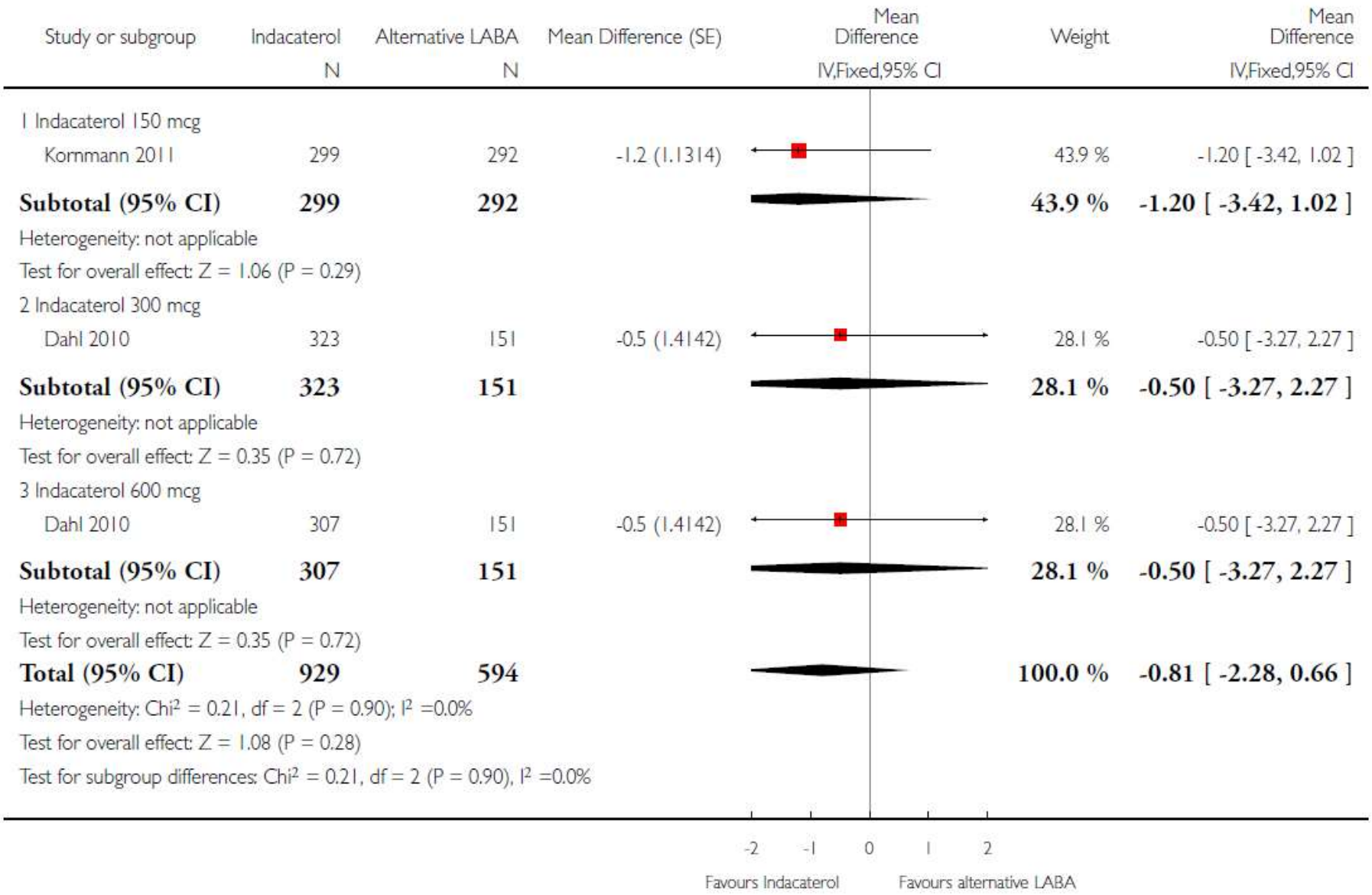
Indacaterol vs twice-daily LABAs

- 13 trials with 9961 participants
  - 10 (n=8562) indacaterol versus placebo
  - 5 (n=4133) indacaterol vs twice-daily β2- agonist
- Primary objectives - trough FEV1 at the end of dosing, exacerbation rates and quality of life. Significant adverse
- Secondary outcomes - events, mortality and dyspnoea

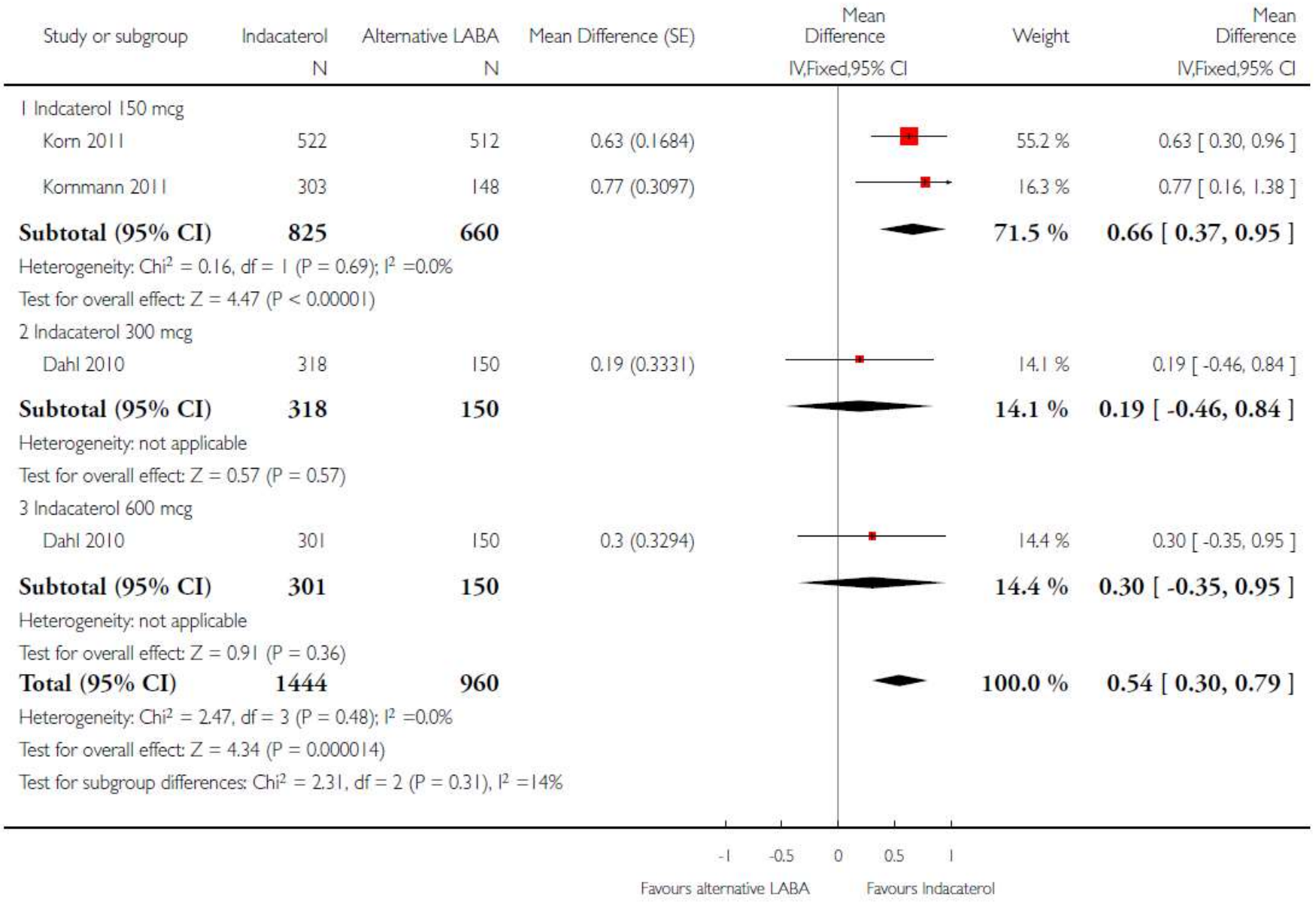
Indacaterol vs LABAs, Outcome - Trough FEV1 (by dose).



Indacaterol vs LABAs, Outcome - Quality of life



Dyspnoea


Study or subgroup
Indacaterol N
Alternative LABA N
Mean Difference (SE)
Mean Difference IV,Fixed,95% CI
Weight
Mean Difference IV,Fixed,95% CI
1 Indcaterol 150 mcg
Korn 2011 522 512 0.63 (0.1684) 55.2 % 0.63 [0.30, 0.96]
Kornmann 2011 303 148 0.77 (0.3097) 16.3 % 0.77 [0.16, 1.38]
Subtotal (95% CI) 825 660 71.5 % 0.66 [0.37, 0.95]
Heterogeneity: Chi² = 0.16, df = 1 (P = 0.69); I² =0.0%
Test for overall effect: Z = 4.47 (P < 0.00001)
2 Indacaterol 300 mcg
Dahl 2010 318 150 0.19 (0.3331) 14.1 % 0.19 [-0.46, 0.84]
Subtotal (95% CI) 318 150 14.1 % 0.19 [-0.46, 0.84]
Heterogeneity: not applicable
Test for overall effect: Z = 0.57 (P = 0.57)
3 Indacaterol 600 mcg
Dahl 2010 301 150 0.3 (0.3294) 14.4 % 0.30 [-0.35, 0.95]
Subtotal (95% CI) 301 150 14.4 % 0.30 [-0.35, 0.95]
Heterogeneity: not applicable
Test for overall effect: Z = 0.91 (P = 0.36)
Total (95% CI) 1444 960 100.0 % 0.54 [0.30, 0.79]
Heterogeneity: Chi² = 2.47, df = 3 (P = 0.48); I² =0.0%
Test for overall effect: Z = 4.34 (P = 0.000014)
Test for subgroup differences: Chi² = 2.31, df = 2 (P = 0.31), I² =14%
-1
-0.5
0
0.5
1
Favours alternative LABA
Favours Indacaterol

Indacaterol vs Tiotropium

- INHANCE Study
- Double-blind, placebo controlled RCT
- Moderate-to-severe COPD
- Indacaterol 150 or 300 µg or placebo, or open-label tiotropium 18 mg, all OD, for 26 wks
- Primary outcome -trough FEV1 at 12 wks
- 1,683 patients
  - age- 63.3 yr; post-bronchodilator FEV1- 56% predicted; FEV1/FVC- 0.53

Results - INHANCE

- Trough FEV1 at Week 12 increased vs placebo by 180 ml with both indacaterol doses and by 140 ml with tiotropium
- Maintained at 26 weeks and when stratified for age, smoking status and ICS use
- Significantly better in terms of TDI
- Similar in terms of SGRQ
- Adverse effect profile similar

Donohue HF et al. Am J Respir Crit Care Med. 2010 Jul 15;182(2):155-62.

Indacaterol vs Tiotropium - Metanalysis

Study	Treatment duration (weeks)	COPD criteria (GOLD)	Number of subjects	Men, %	Age (mean)	Drug and Dose	Baseline FEV_1 L (% Predicted)	Primary outcome
Donohue et al 2010 (INHANCE study)	26	Moderate to Severe	416	62	63.4	Indacaterol 150µg	1.52 (56.1)	Trough FEV1 at week 12
			415	65	64.0	Tiotropium 18µg	1.45 (53.9)	
Buhl et al 2011 (INTENSITY study)	12	Moderate to Severe	794	70	63.6	Indacaterol 150µg	1.53 (54.6)	Trough FEV1 at week 12
			799	67	63.4	Tiotropium 18µg	1.52 (54.3)	
Bateman et al 2013 (SHINE study)	26	Moderate to Severe	476	74	63.6	Indacaterol 150µg	1.5 (54.9)	Trough FEV1 at week 26
			480	75	63.5	Tiotropium 18µg	1.5 (55.1)	
Decramer et al 2013 (INVIGORATE study)	52	Severe	1721	78	64.0	Indacaterol 150µg	1.13 (40.2)	Trough FEV1 at week 12
			1718	76	64.0	Tiotropium 18µg	1.14 (40.7)	

Kim, J. S et al. PLoS ONE; 2015; 10(3), e0119948

Study name	Sample size		Statistics for each study		
	Indacaterol	Tiotropium	Diff in means	Std diff in means and 95% CI	*P*-Value
Donohue et al 2010	389	393	0.040	0.099 (-0.041, 0.239)	0.166
Buhl et al 2011	794	799	0.010	0.035 (-0.063, 0.134)	0.480
Bateman et al 2013	476	480	0.020	0.060 (-0.067, 0.187)	0.356
Decramer et al 2013	1450	1467	-0.011	-0.036 (-0.109, 0.037)	0.331
Total (95% CI)	3109	3139	0.003	0.014 (-0.036, 0.063)	0.587

Heterogeneity: Tau2 = 0.001, df = 3 (*P* = 0.270) ; I^2 = 23.5%

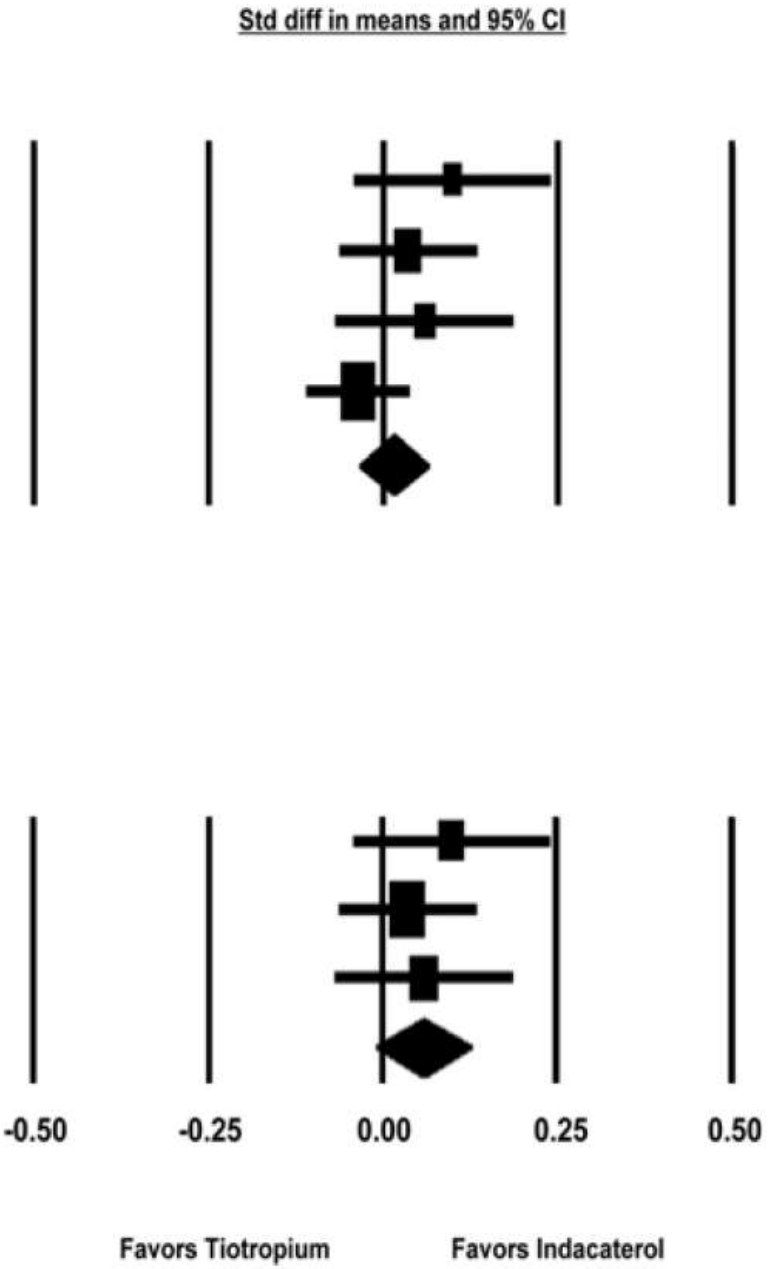
Test for overall effect: Z = 0.54 (*P* = 0.587)

Without Decramer study

	Indacaterol	Tiotropium	Diff in means	Std diff in means and 95% CI	*P*-Value
Donohue et al 2010	389	393	0.040	0.099 (-0.041, 0.239)	0.166
Buhl et al 2011	794	799	0.010	0.035 (-0.063, 0.134)	0.480
Bateman et al 2013	476	480	0.020	0.060 (-0.067, 0.187)	0.356
Total (95% CI)	1659	1672	0.017	0.057 (-0.011, 0.125)	0.098

Heterogeneity: Tau^2 = 0, df = 2 (*P* = 0.766) ; I^2 = 0%

Test for overall effect: Z = 1.65 (*P* = 0.098)



Kim, J. S et al. PLoS ONE; 2015; 10(3), e0119948

Indacaterol vs Tiotropium

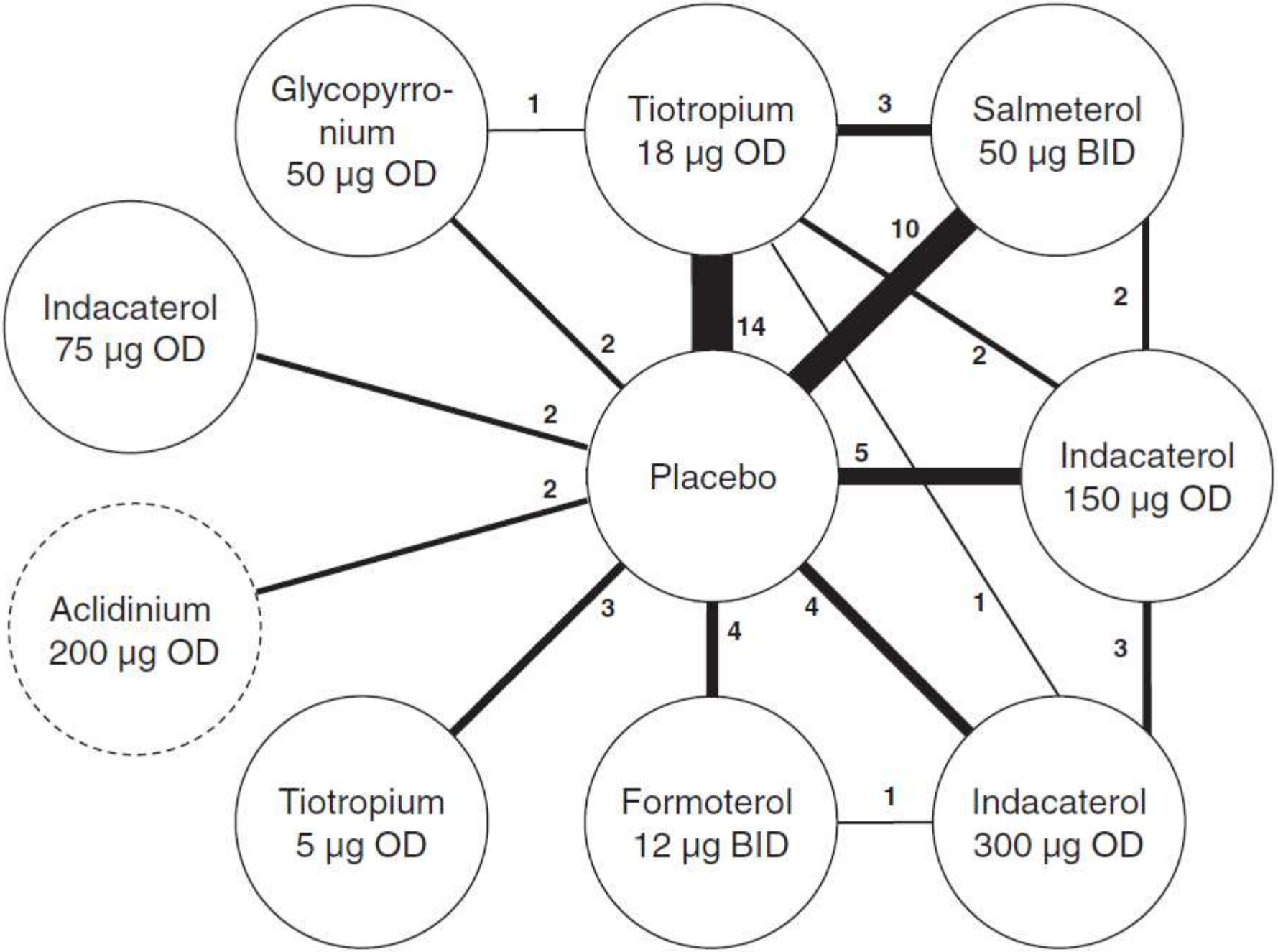
- Similar SGRQ profile
- Incidences of nasopharyngitis, serious cardiovascular events, and serious adverse events similar
- Cough (OR = 1.68, P < 0.001, and RR = 1.63) and COPD worsening (OR = 1.18, P = 0.003, and RR = 1.12) were higher for indacaterol than tiotropium
- Without INVIGORATE study, the difference in the incidence of COPD worsening became non-significant (OR = 1.13, P = 0.204, and RR =1.09)

Kim, J. S et al. PLoS ONE; 2015; 10(3), e0119948

Comparative efficacy of long-acting bronchodilators for COPD - a network meta-analysis

- Evaluate the comparative efficacy of
  - indacaterol 75/150/300 µg OD
  - glycopyrronium bromide 50 µg OD
  - tiotropium bromide 18 µg OD
  - salmeterol 50 µg BD
  - formoterol 12 µg BD
  - Placebo
- Moderate to severe COPD
- 40 RCTs combined in a Bayesian network meta-analysis

Cope et al. Respiratory Research 2013, 14:100



Cope et al. Respiratory Research 2013, 14:100

Results

- Indacaterol was associated with a higher trough FEV1 than other active treatments
  - difference for indacaterol 150 µg and 300 µg vs placebo: 152 mL and 160 mL
- Indacaterol was associated with greatest improvement in SGRQ score
  - difference for indacaterol 150 µg and 300 µg vs placebo: -3.9 and-3.6
- Glycopyrronium and tiotropium 18 µg resulted in the next best estimates for both outcomes with minor differences

Cope et al. Respiratory Research 2013, 14:100

A UK-Based Cost-Utility Analysis of Indacaterol, A Once-Daily Maintenance Bronchodilator for Patients with COPD, Using Real World Evidence on Resource Use

- To establish, from the NHS perspective, the cost-effectiveness profile of indacaterol compared with tiotropium and salmeterol, in patients with moderate to severe COPD

- Took clinical inputs from INHANCE and INLIGHT-2 trials

Price D et al. Appl Health Econ Health Policy, 2013; 11:259–274

Cost-effectiveness results for indacaterol for a 3-year time horizon

	Indacaterol 150 µg	**Tiotropium 18 µg**	**Difference**
Total costs	£4534	£4781	−£248
Total QALYs	2.158	2.150	0.008
ICER			Dominant[a]
	Indacaterol 150 µg	**Salmeterol 2 × 50 µg**	**Difference**
Total costs	£4583	£4692	−£110
Total QALYs	2.158	2.149	0.008
ICER			Dominant[a]
	Indacaterol 300 µg	**Tiotropium 18 µg**	**Difference**
Total costs	£4501	£4760	−£259
Total QALYs	2.162	2.151	0.011
ICER			Dominant[a]

[a] Dominant = less cost, better outcomes

ICER incremental cost-effectiveness ratio, *QALY* quality-adjusted life-years

A real-world evaluation of indacaterol and other bronchodilators in COPD: the INFLOW study

- Prospective, noninterventional study assessing the effectiveness and safety of LABAs in COPD from the Middle East, Asia, and South Africa

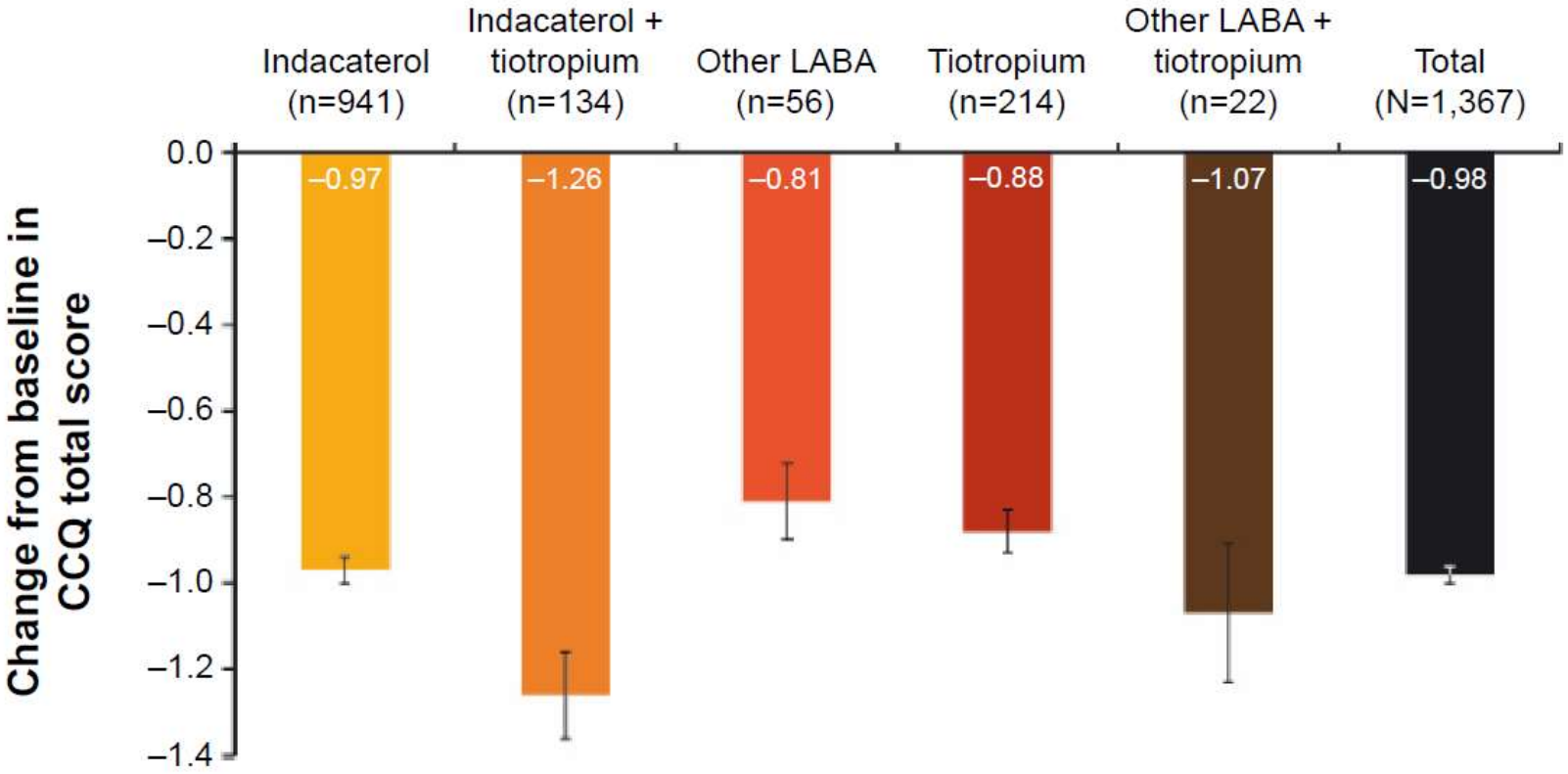
- Patients newly prescribed or switched to indacaterol or other LABA, or tiotropium (monotherapy or in combination) were evaluated over 6 months
- Primary endpoint - clinical COPD questionnaire overall score at the end of the study

Juvelekian G et al. Int J Chron Obstruct Pulmon Dis. 2015; 10: 2109–2120.

Results

- 1,710 patients (mean postbronchodilator FEV1, 59% predicted)
  - indacaterol (n=1,179)
  - Other LABA (n=68)
  - Tiotropium (n=271)
  - Indacaterol plus tiotropium (n=167)
  - Other LABA plus tiotropium (n=25)

Juvelekian G et al. Int J Chron Obstruct Pulmon Dis. 2015; 10: 2109–2120.



- Indacaterol scored high on patient satisfaction rating

Juvelekian G et al. Int J Chron Obstruct Pulmon Dis. 2015; 10: 2109–2120.

Approved dose

- US – 75mcg OD
- Europe – 150 and 300 mcg OD
- India
  - Onbrez Breezhaler 150mcg Capsule
  - Novartis India
  - INR 2031.00

Olodaterol

- Chirally pure
- Potent, highly selective inhaled ultra-LABA
- Sustained duration of activity
- Rapid onset
- 241-fold greater selectivity for β2 over β1-adrenoceptors
- Demonstrates greater potency than indacaterol, with an efficacy of 88% relative to isoprenaline
- Boehringer Ingelheim®

Bouyssou T, et al. J Pharmacol Exp Ther. 2010;334(1):53–62

Olodaterol - Sustained action

- Does not appear to be due to lipophilicity
- A portion of the delivered molecules form semi-stable complexes with the receptor and its G-coupled protein
- T1/2 - 17 h

Casarosa P, et al. J Pharmacol Exp Ther. 2011;337:600–609

Safety and efficacy

Ferguson et al

- N= 624 and 642
- Olodaterol 5 or 10 mg with placebo
- Significant ($p < 0.0001$) improvements at 12 weeks with once-daily olodaterol versus placebo use in the lung function coprimary endpoints
  - FEV1 AUC from 0 to 3 hours
  - Trough FEV1
- No significant differences between 2 doses
- COPD control better

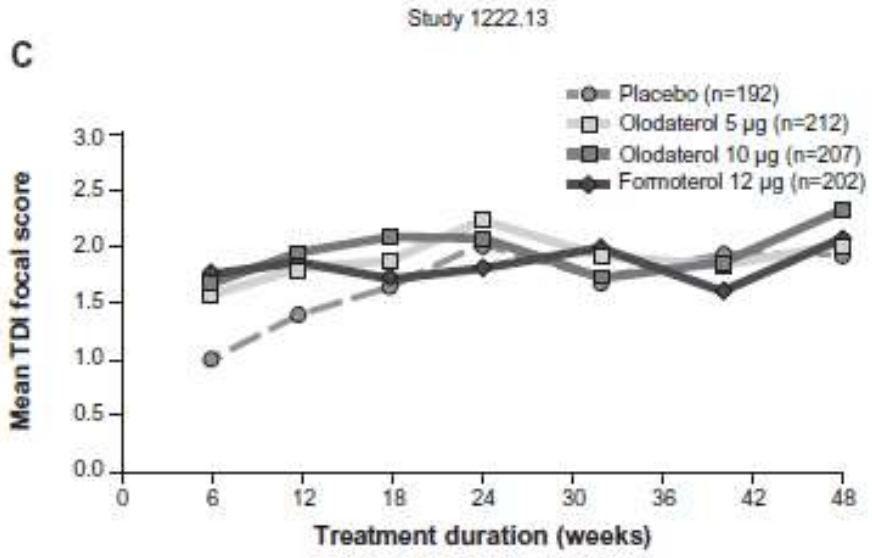
Koch et al

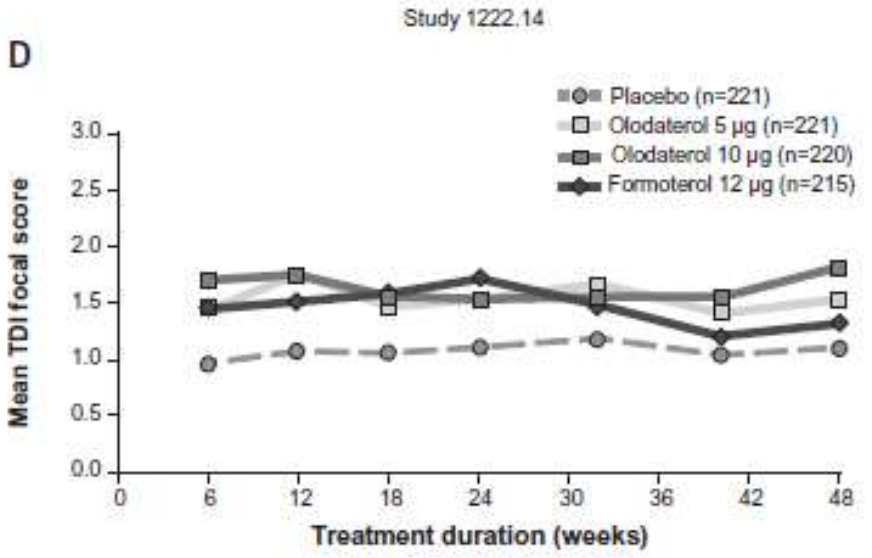
- N = 904 and 934
- Formoterol, olodaterol 5 mg or 10 mg, and placebo
- Lung function co-primary endpoints – similar results

•*Ferguson et al. Int J Chron Obstruct Pulmon Dis. 2014;9:629–645*

•*Koch et al. Int J Chron Obstruct Pulmon Dis. 2014;9:697–714*

Adjusted mean TDI focal score over 48 weeks of treatment





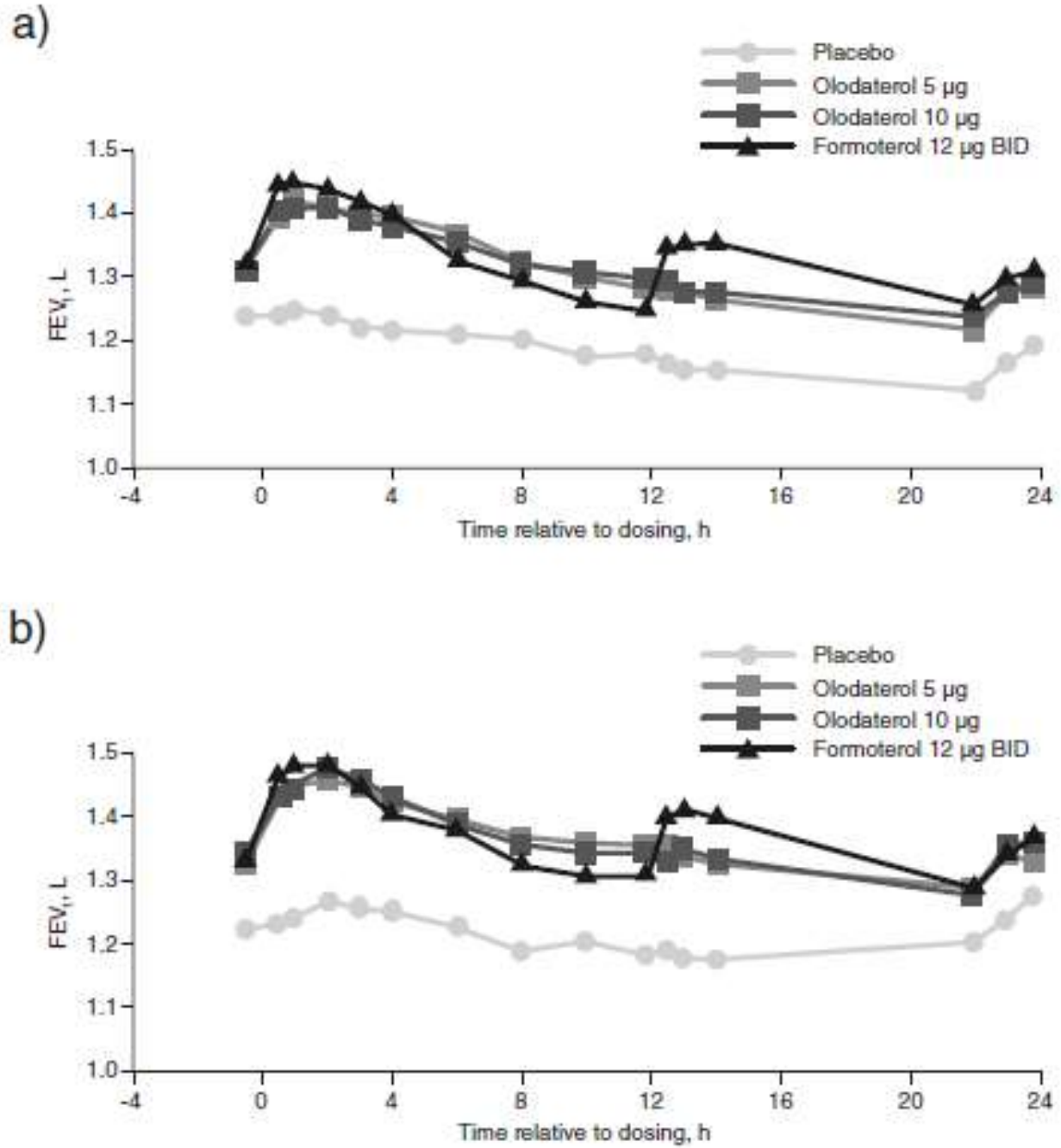
- After adjustment, Olodaterol but not indacaterol improved TDI and SGRQ.

•*Koch et al. Int J Chron Obstruct Pulmon Dis. 2014;9:697–714*

The 24-h FEV_1 time profile of olodaterol once daily via Respimat® and formoterol twice daily via Aerolizer® in patients with GOLD 2–4 COPD: results from two 6-week crossover studies

- 2 replicate, randomized, double-blind, double-dummy, four-way crossover studies
- Olodaterol 5 and 10 µg QD, formoterol 12 µg BID, or placebo for 6 weeks
- N=199 (99+100)
- Co-primary end points
  - FEV1 area under the curve from 0–12 h ($AUC_{0–12}$) response (change from baseline)
  - FEV1 AUC from 12–24 h ($AUC_{12–24}$) response after 6 weeks
- Secondary endpoint - FEV1 AUC from 0–24 h response

Feldman et al. SpringerPlus 2014, 3:419



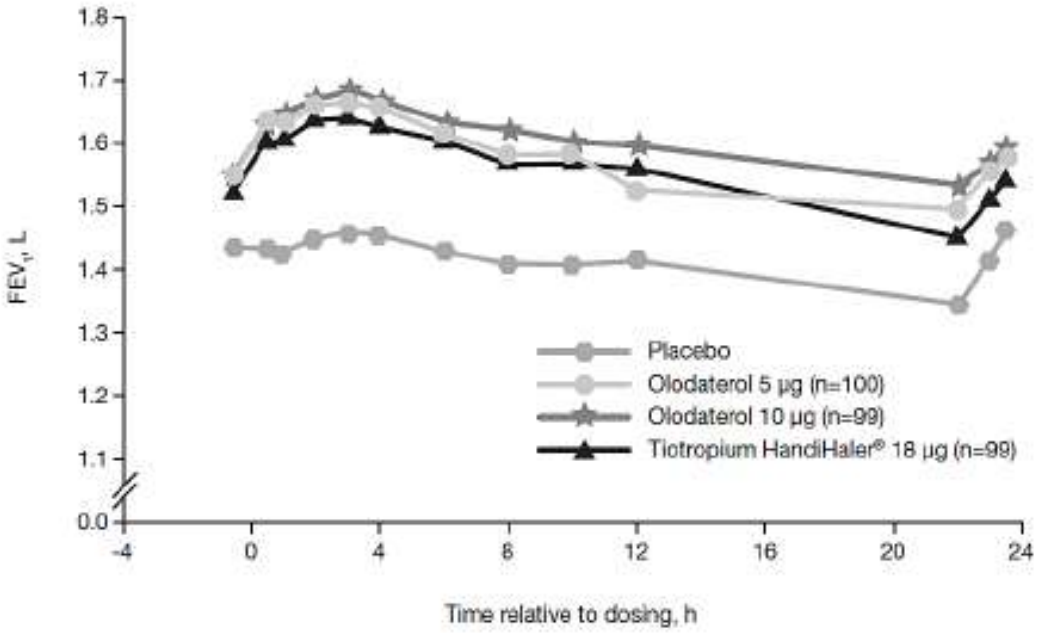
Feldman et al. SpringerPlus 2014, 3:419

The 24 Hour Lung Function Time Profile of Olodaterol Once Daily Versus Placebo and Tiotropium in Patients with Moderate to Very Severe Chronic Obstructive Pulmonary Disease

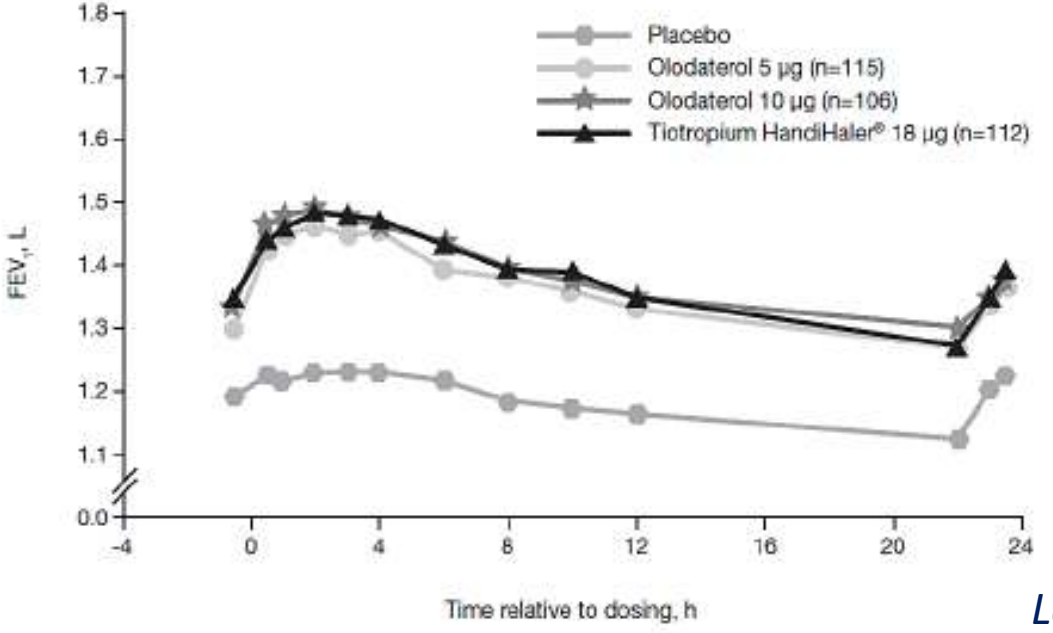
- 2 replicate, randomized, double-blind, four-way crossover (6-wk treatment periods)trials
  - Olodaterol (5 and 10 µg) once daily (via Respimat®)
  - Tiotropium 18 µg via HandiHaler®)
  - Placebo
- 230 patients (108+122)
- Co-primary end points
  - FEV1 area under the curve from 0–12 h ($AUC_{0–12}$) response (change from baseline)
  - FEV1 AUC from 12–24 h ($AUC_{12–24}$) response after 6 weeks
- Secondary endpoint - FEV1 AUC from 0–24 h response

Lange et al., J Pulm Respir Med 2014, 4:4

a)



b)



Lange et al., J Pulm Respir Med 2014, 4:4

Indacaterol vs Olodaterol

- Indirect treatment comparison by systematic review and synthesis of the available clinical evidence
- 18 trials taken (8, olodaterol; 10, indacaterol)
- Network meta-analysis and adjusted indirect comparison methods
- Outcomes - trough FEV1, TDI, SGRQ, rescue medication use, and exacerbations

Roskell NS, et al. Int J Chron Obstruct Pulmon Dis. 2014; 9:813-24.

Differences - heterogeneity

Olodaterol studies

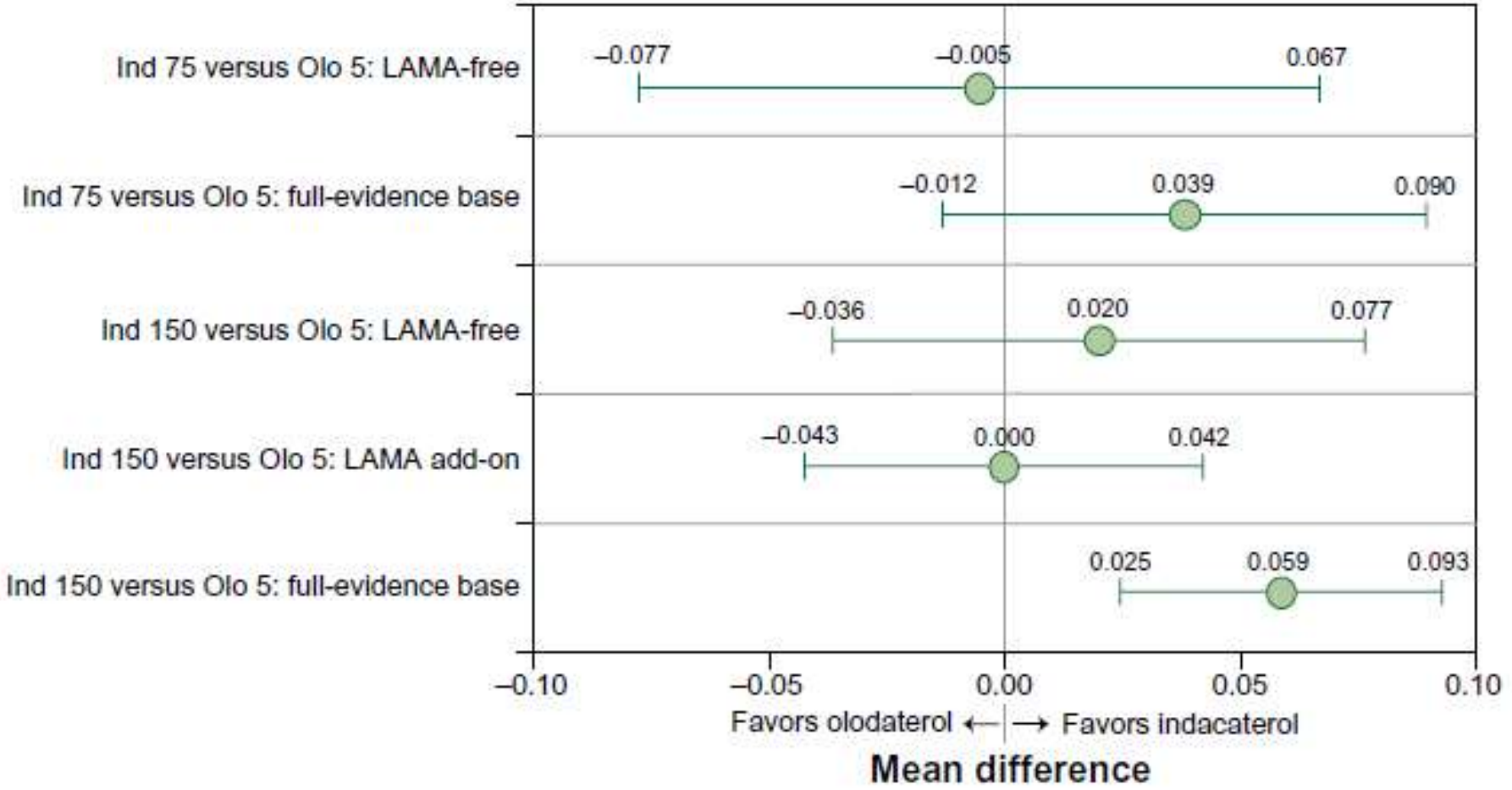
- Allowed concomitant use of bronchodilators, ICS, and xanthines
- Moderate to very severe COPD

Indacaterol studies

- Allowed concomitant use of ICS but not bronchodilators or xanthines
- Moderate-to-severe COPD

- LAMA-free analysis
- LAMA add-on analysis
- Sensitivity analysis

Roskell NS, et al. Int J Chron Obstruct Pulmon Dis. 2014; 9:813-24.



- No difference in TDI and SGRQ in any group

Roskell NS, et al. Int J Chron Obstruct Pulmon Dis. 2014; 9:813-24.

Delivery device - Respimat

Vilanterol

- Potent, selective inhaled ultra-LABA
- Greater potency than indacaterol and salbutamol
- Significantly greater β2-selectivity than formoterol, indacaterol, or salbutamol
- Highly lipophilic - inherent DOA > 24 h
- Onset- 5 min; median time to maximum plasma levels following inhalation -10 min

Monaco TJ et al. Expert Opin Emerg Drugs. 2017 Sep;22(3):285-299.

Vilanterol

- Phase IIb multicenter, randomized dose-ranging trials
- 25 µg and 50 µg produced clinically relevant increases in FEV1 > 130 ml
  - 137 and 165 ml, respectively
- No significant AEs
  - most common hypokalemia and hyperglycemia
- Developed by Theravance®

Hanania NA, et al. Chest. 2012;142:119–127

Abediterol (formerly LAS100977)

- Greater affinity to β2-adrenoceptor than salmeterol, formoterol, or indacaterol
- B2:β1 greater than formoterol and indacaterol
- More sustained duration of action (t½ = 669 min) than indacaterol (t½ = 449 min), salmeterol (t½ = 230 min), formoterol (t½ = 76 min)
- Rapidity of onset second only to formoterol
- Acquired from Almirall® by AstraZeneca® in 2014

Aparici M, et al. J Pharm Exp Therap. 2012 Aug;342 (2):497–509

Comparative Pharmacokinetics of Ultra-LABAs

Variable	Olodaterol	Indacaterol	Vilanterol
t_{max} (min)	10–20	15	5–15
Time to steady state (days)	8	12–15	6
$t_{½}$ (hr)	7.5	45.5–126.0	11.0
Bioavailability (%)	~30	43–45	27
Protein binding after i.v. administration (%)	60	95	94
V after i.v. administration (L)	1110	2360–2560	165
Metabolism	Direct glucuronidation and *O*-demethylation (substantially); CYP2C9, CYP2C8, and CYP3A4 (negligibly); uridine diphosphate glycosyl transferase isoforms	Uridine diphosphate glycosyl transferase isoform UGT1A1, CYP3A4 (hydroxylation mainly), CYP1A1, CYP2D6	CYP3A4, P-gp transporter substrate
Elimination	Urine (5–7% unchanged)	Feces (54% unchanged, 23% hydroxylated metabolites), urine (<2%)	Feces (30%), urine (70%)

Monaco TJ et al. Expert Opin Emerg Drugs. 2017 Sep;22(3):285-299.

Bifunctional MABA agents

- 'Bi-functional molecules' with both muscarinic antagonism and β-agonism domains
- Batefenterol (GSK961081, formerly TD-5959) by Theravance® and GlaxoSmithKline®
- Animal studies have shown success
- Phase IIb 4-week dosing trial in moderate-to-severe COPD
  - 400 µg daily dose of batenfenterol elicited greater bronchodilation than salmeterol
- 2-week trial compared batenfenterol 400 µg OD to combination tiotropium OD and salmeterol BD
  - MABA induced similar bronchodilation to combination therapy with a more rapid onset of action

- *Wielders PLML, et al. Eur Respir J. 2013;42:972–981.*
- *Bateman ED, et al. Pulm Pharmacol Ther. 2013 Oct;26(5):581–587.*

Combinations

Medication/Formulation	Class	Approved
Vilanterol/umeclidinium bromide inhalation powder	LABA+LAMA	Dec 2013
Fluticasone furoate/vilanterol inhalation powder	ICS+LABA	May 2013
Indacaterol +glycopyrrolate inhalation powder	LABA+LAMA	Oct 2015
Tiotropium/olodaterol inhalation spray	LAMA+LABA	Apr 2015

Monaco TJ et al. Expert Opin Emerg Drugs. 2017 Sep;22(3):285-299.

Combinations

- UltraLABA + LAMA
- UltraLABA + ICS

Pharmacological LVRS?

Molino et al

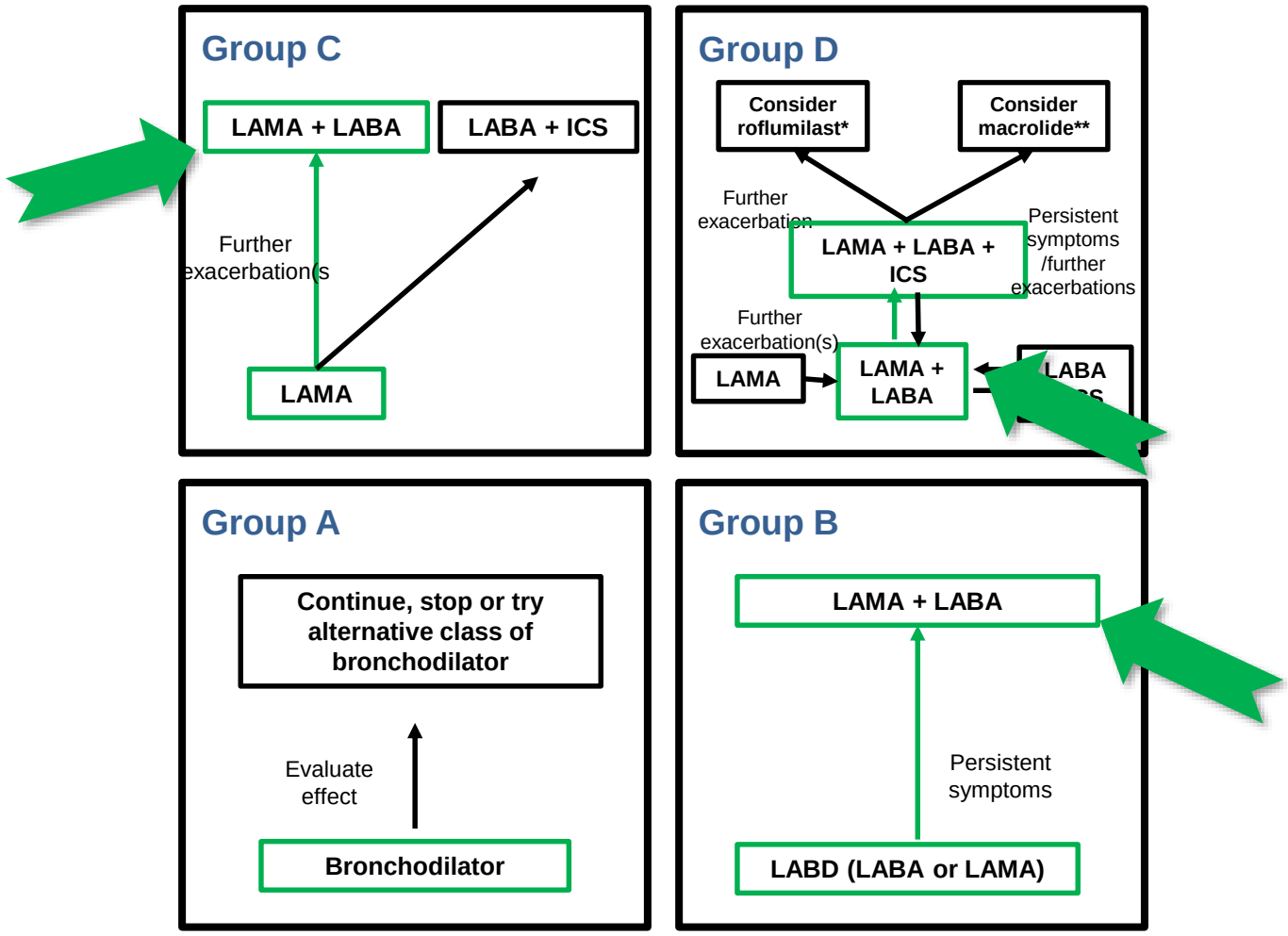
- 40 patients were monitored with forced oscillation technique and spirometry
- Indacaterol/Glycopyrronium vs Tiotropium
- Small airway function and IC significantly better with combination

Salomon et al

- 78 pts; spirometry and body plethysmography
- Combination vs indacaterol
- Significantly better IC, FEV1, FVC, Resistace but not TLC

Molino et al. Multidisciplinary Respiratory Medicine. 2017;12:25
Salomon et al. Respiratory Research. 2017;18:13

According to GOLD 2017, dual bronchodilation is the 'preferred choice' for most COPD patients



Indacaterol+Glycopyronium

A2339 RADIATE
Long-term safety
(vs tiotropium and placebo)

A2331 LANTERN
China safety and efficacy
(vs fluticasone/salmeterol and placebo)

A2318 FLAME
Long-term exacerbations
(vs
fluticasone/salmeterol)

A2307 ENLIGHTEN
Long-term safety
(vs placebo)

2326 BEACON
Non-inferiority vs
free combination

2313 ILLUMINATE
FEV_1, TDI, SGRQ
(vs fluticasone/salmeterol)

1301 ARISE
Japan pivotal safety
(vs tiotropium)

2305 BRIGHT
Exercise tolerance
(vs tiotropium and placebo)

A2303 SHINE
FEV_1, TDI, SGRQ,
(vs monocomponents,
tiotropium and placebo)

A2304 SPARK
Exacerbations
(vs glycopyrronium and
tiotropium)

2322 BLAZE
TDI/BDI
(vs tiotropium)

Effect of QVA149 on lung volumes and exercise tolerance in COPD patients: The BRIGHT study☆

- Moderate-to-severe COPD were randomized to QVA149 110/50 mg, placebo or tiotropium 18 mg once daily in a blinded, 3-period crossover study for 3 weeks
- Primary endpoint - exercise endurance time at Day 21 for QVA149 versus placebo
- 85 patients were randomized; 86% completed the study
- QVA149 significantly improved exercise endurance time at Day 21 compared with placebo but wasn't superior to Tiotropium

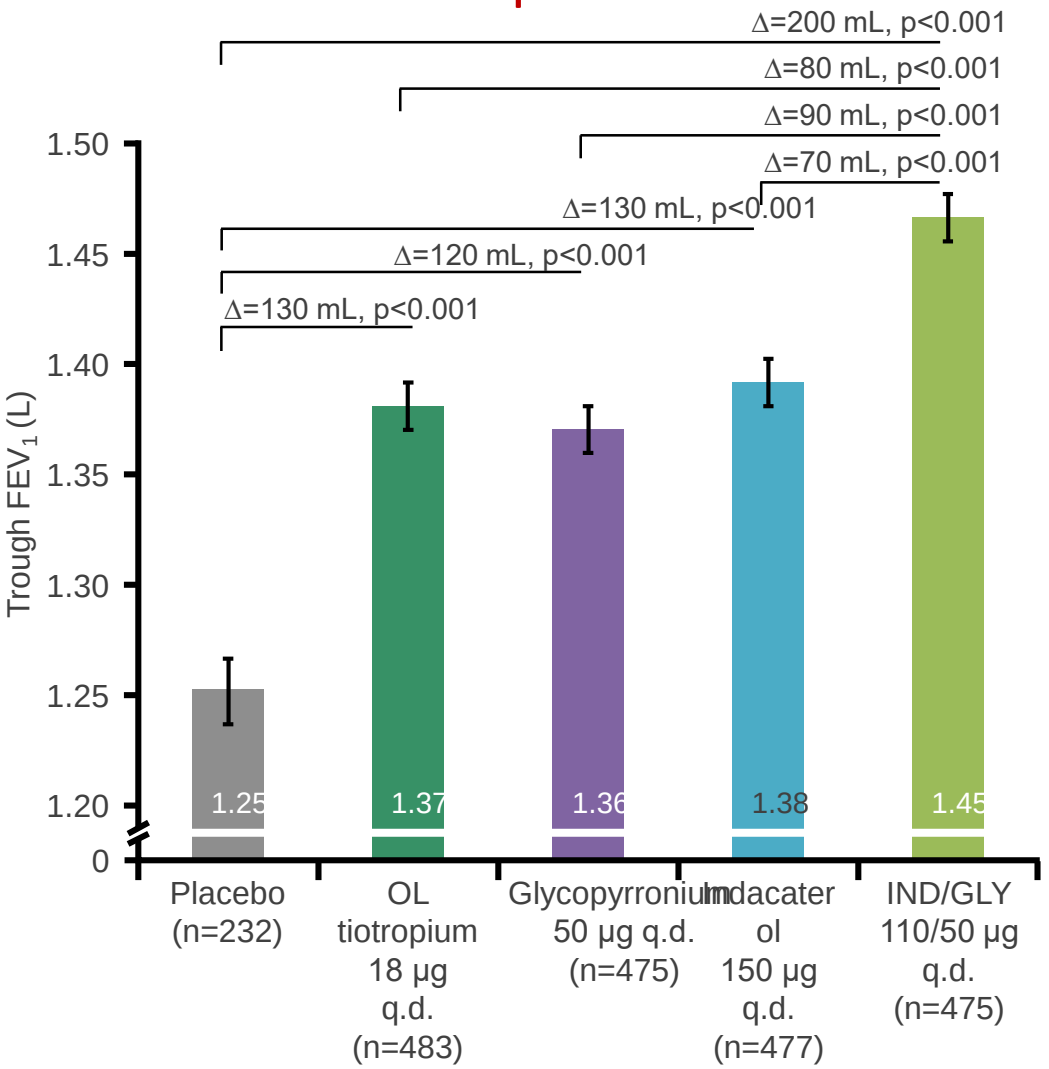
Beeh KM et al. Respir Med. 2014;108(4):584-92

SHINE Study

- Pivotal safety and efficacy study (USA, EU, Latin America, Asia)
- 2,144 COPD patients randomized; 2,135 analysed
- 26-week, multicenter, randomized, double-blind, parallel-group, placebo and active-controlled (open-label tiotropium) study
- Randomised (2:2:2:2:1) to receive once-daily QVA149 (indacaterol 110mcg/glycopyrronium 50 mcg), indacaterol 150 mcg, glycopyrronium 50 mcg, open-label tiotropium 18 mcg or placebo
- Primary end-point – trough FEV1 at week 26 for QVA149 versus its monocomponents

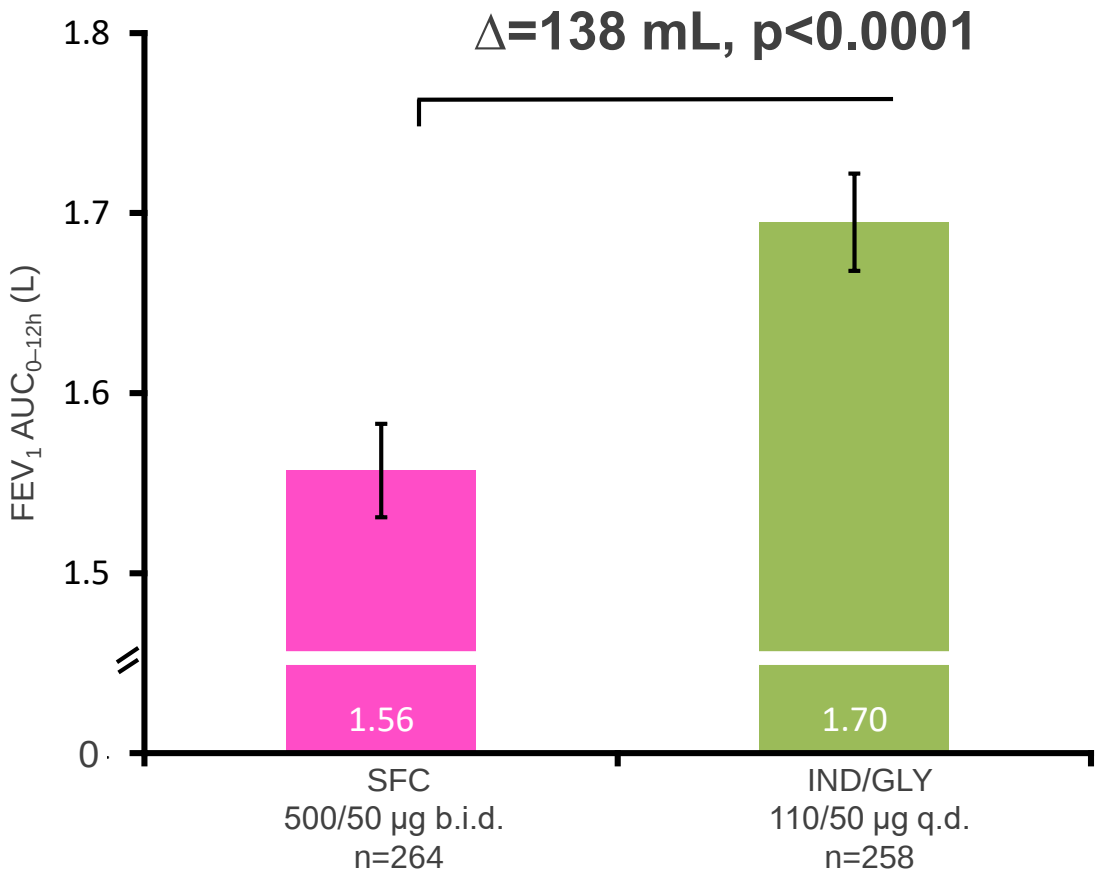
Bateman et al. Eur Respir J 2013; 42: 1484–1494

SHINE: IND/GLY significantly improved lung function vs monocomponents and TIO at Week 26



Bateman et al. Eur Respir J 2013; 42: 1484–1494

ILLUMINATE: IND/GLY FDC improved lung function (FEV1 AUC0–12h) at Week 26 vs SFC



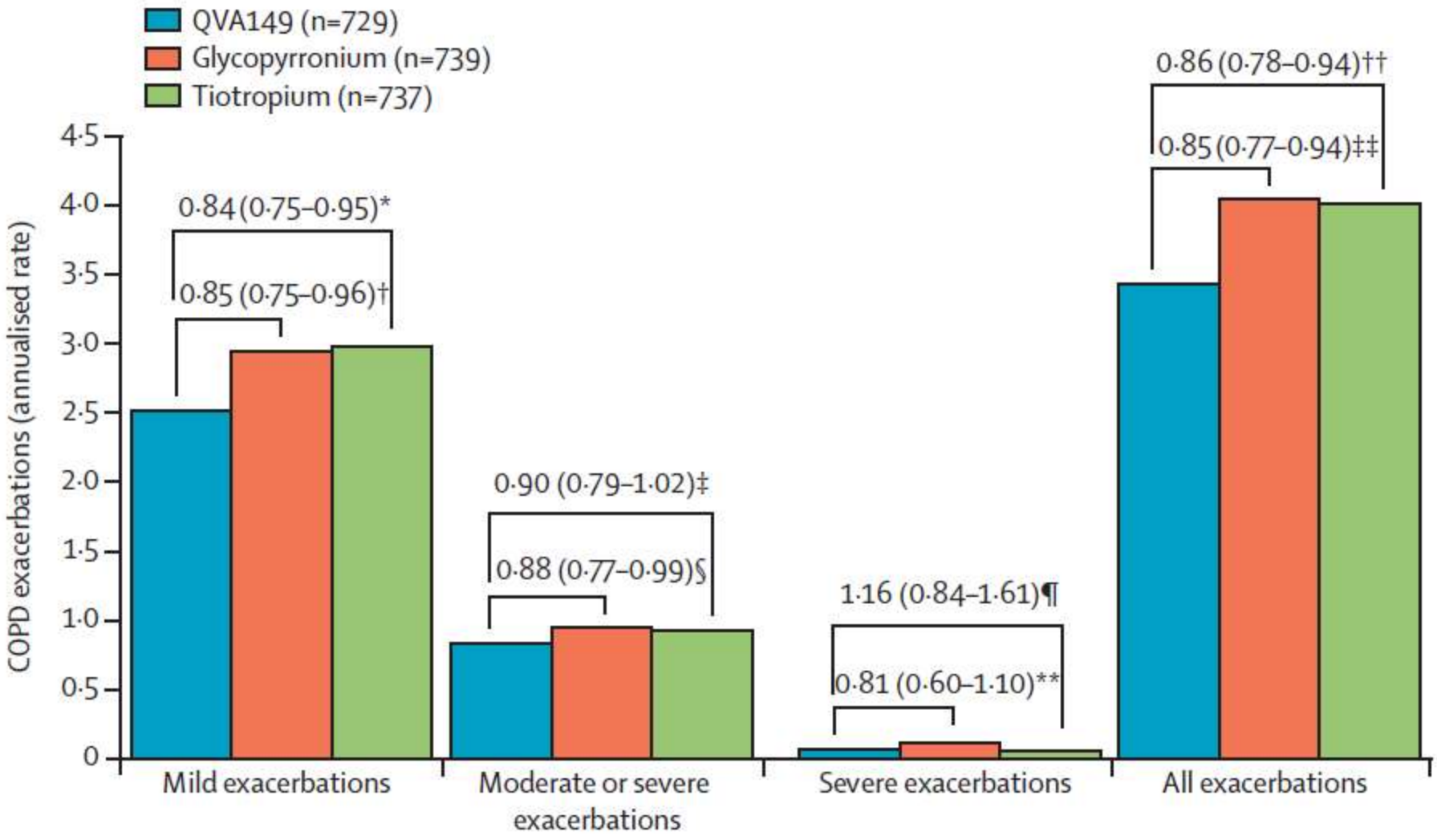
Vogelmeier et al. Lancet Respir Med 2013

Summary of studies

IND/GLY vs fluticasone/salmeterol		IND/GLY vs tiotropium
Breathlessness: difference in TDI score [1] +0.76 (p=0.003)	**PATIENT REPORTED OUTCOMES**	Breathlessness: difference in TDI score [3] +0.49 (p=0.021)
Reduction in reliever medication use [1] −0.39 puffs per day (p=0.019)		Days able to perform daily activities [4] +8.45% (p<0.001)
Health status: difference in SGRQ score [1] −1.24 (p=NS)		Reduction in reliever medication use [4] −0.54 puffs per day (p<0.001)
		Health status: difference in SGRQ score [4] −2.13 (p=0.009)
Onset of action: FEV_1 at 5 min [1] +150 mL (p<0.001)	**IMPROVEMENT IN LUNG FUNCTION**	**Onset of action: FEV_1 at 5 min [4] +120 mL (p<0.001)**
Peak FEV_1 [1] +155 mL (p<0.001)		Peak FEV_1 [4] +130 mL (p<0.001)
24-hour efficacy: trough FEV_1 [2] +75 mL (p<0.001)		24-hour efficacy: trough FEV_1 [4] +80 mL (p<0.001)

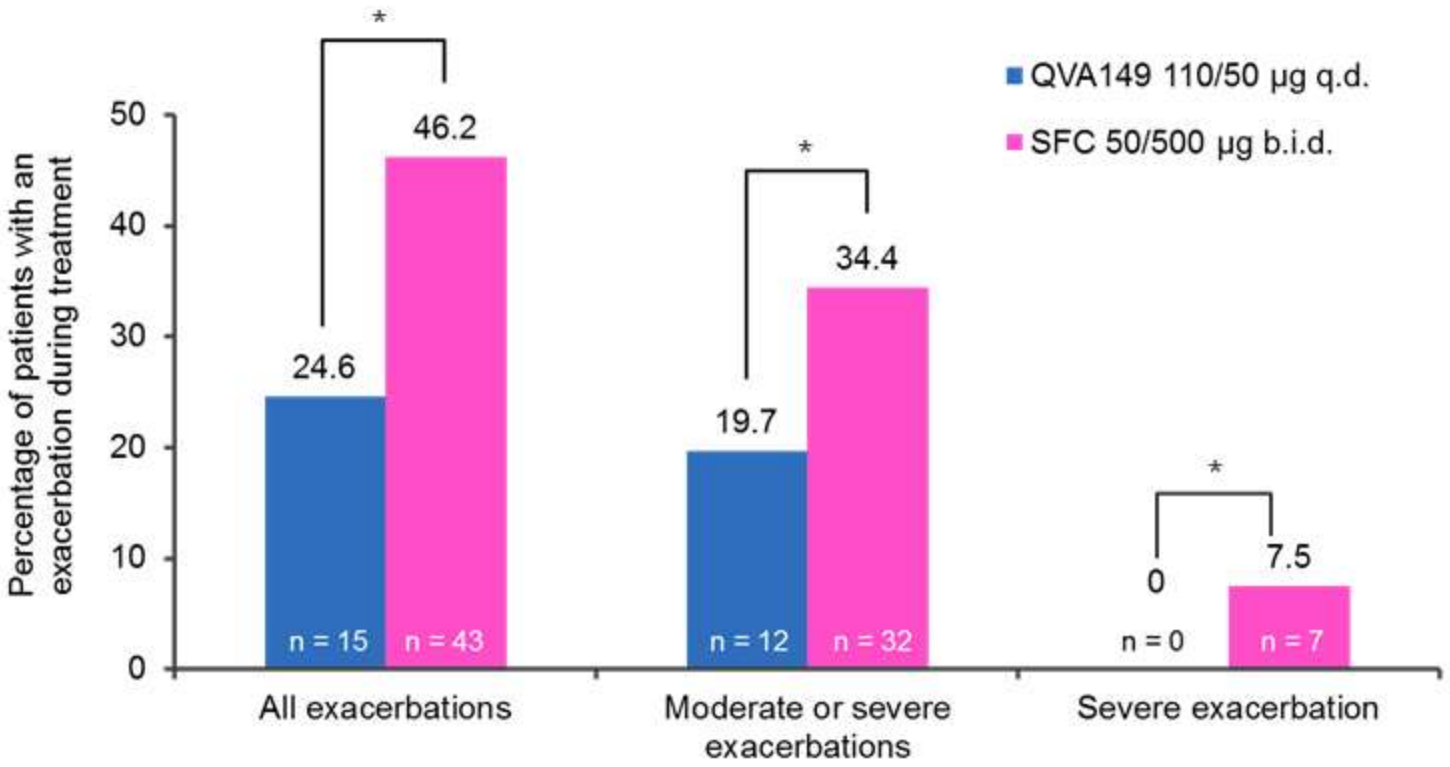
1. Vogelmeier et al. Lancet Respir Med 2013 (ILLUMINATE) ; 2. Zhong et al. Int J COPD 2015 (LANTERN) ; 3. Mahler et al. Eur Respir J 2014 (BLAZE); 4. Bateman et al. Eur Respir J 2013(SHINE)

SPARK: IND/GLY reduced the rate of all exacerbations vs GLY and TIO over 64 weeks



Wedzicha et al. Lancet Respir Med 2013

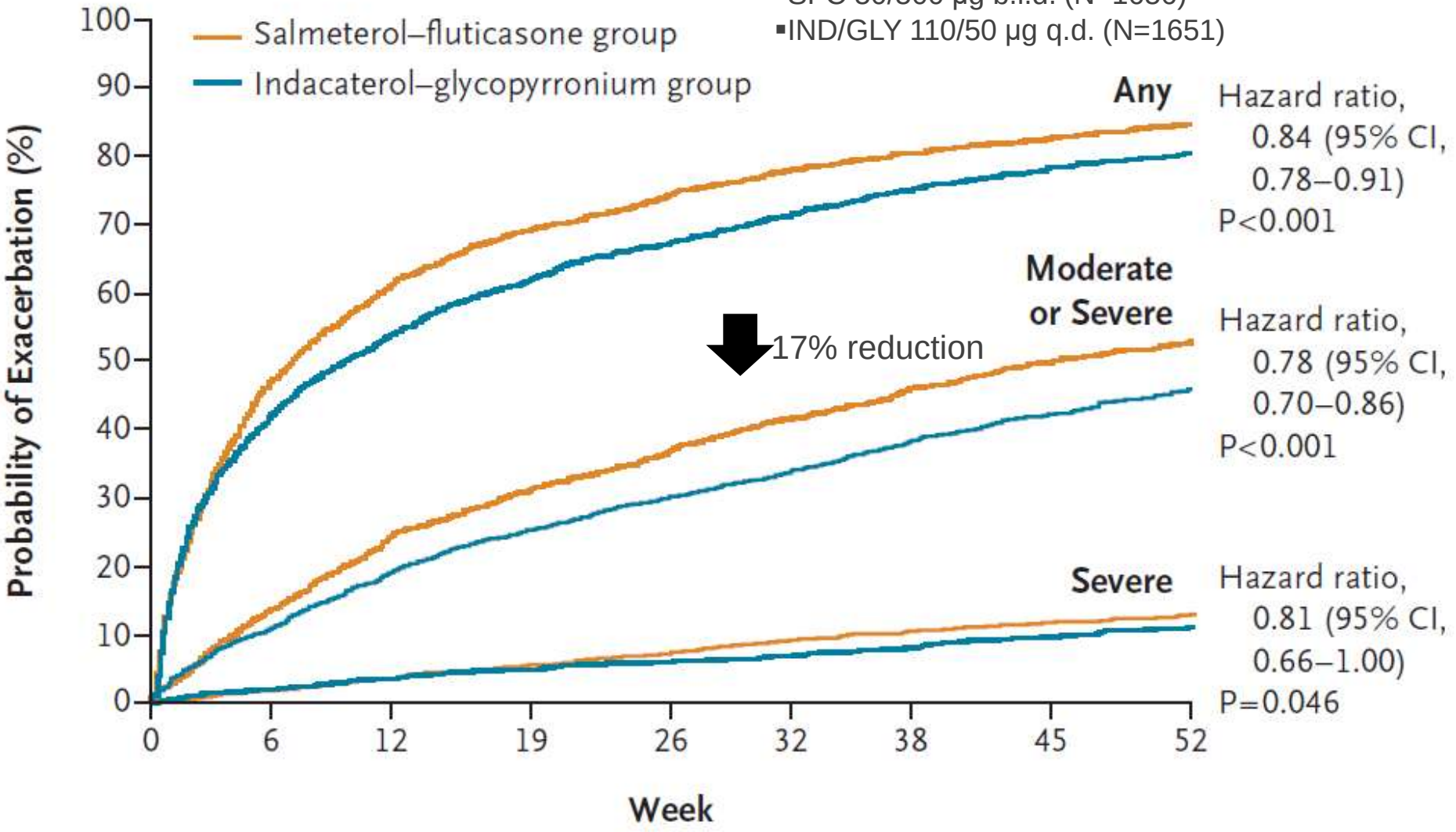
Efficacy and safety of IND/GLY vs SFC – LANTERN : Exacerbations in patients with a history of exacerbations



N Zhong et al. Int J COPD 2015; 10:1015-26

A 52-week treatment, multi-center, randomized, double-blind, double dummy, parallel-group, active controlled study to compare the effect of Ind/Gly (indacaterol maleate / glycopyrronium bromide) with salmeterol/fluticasone on the rate of exacerbations in subjects with moderate to very severe COPD

- SFC 50/500 µg b.i.d. (N=1656)
- IND/GLY 110/50 µg q.d. (N=1651)

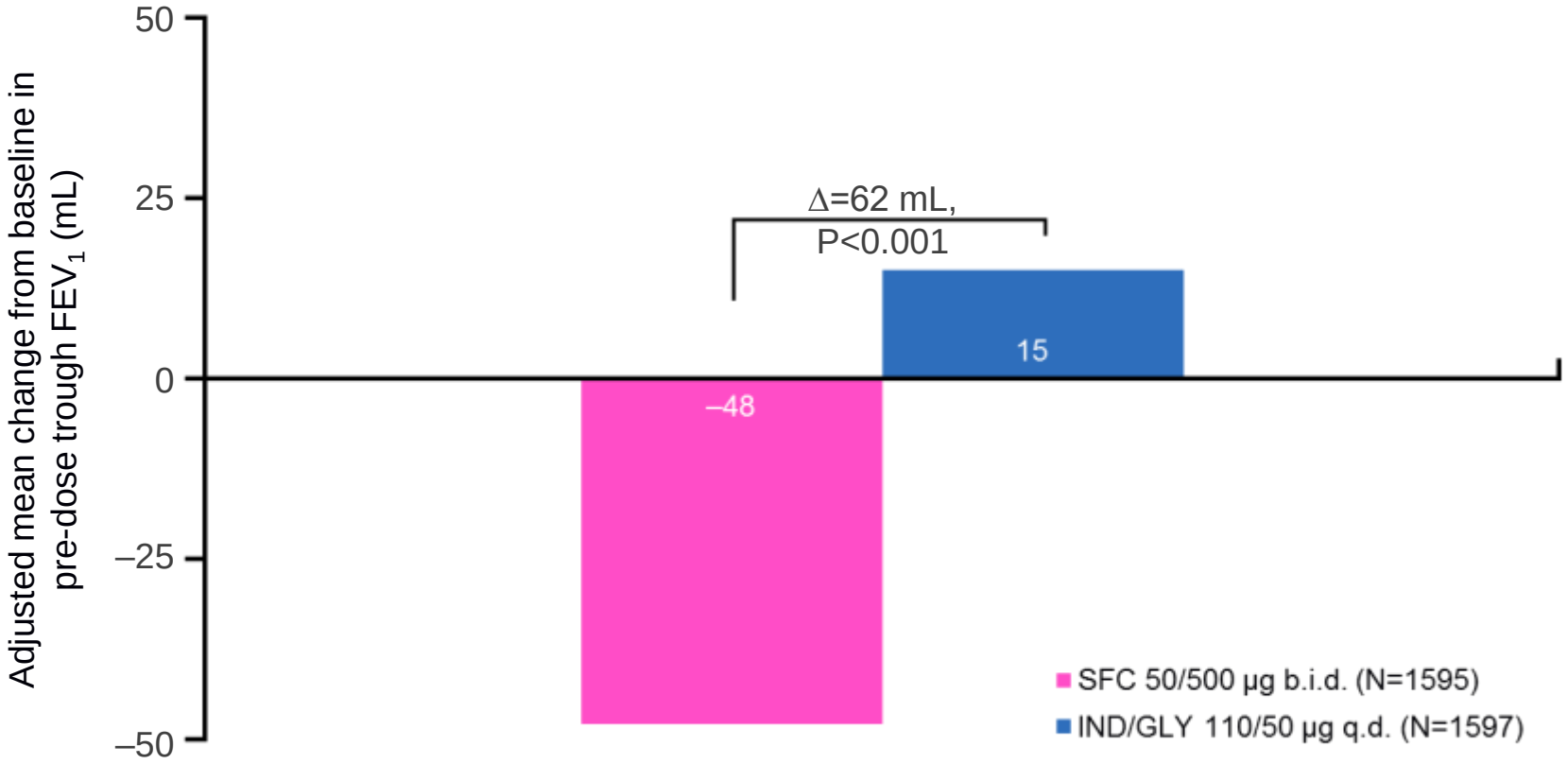


Risk reduction for Time to first exacerbation

- **All exacerbations:** 16% risk reduction
- **Moderate or severe exacerbation:** 22% risk reduction (prolonged by 40 days)
- **Severe exacerbation:** 19% risk reduction

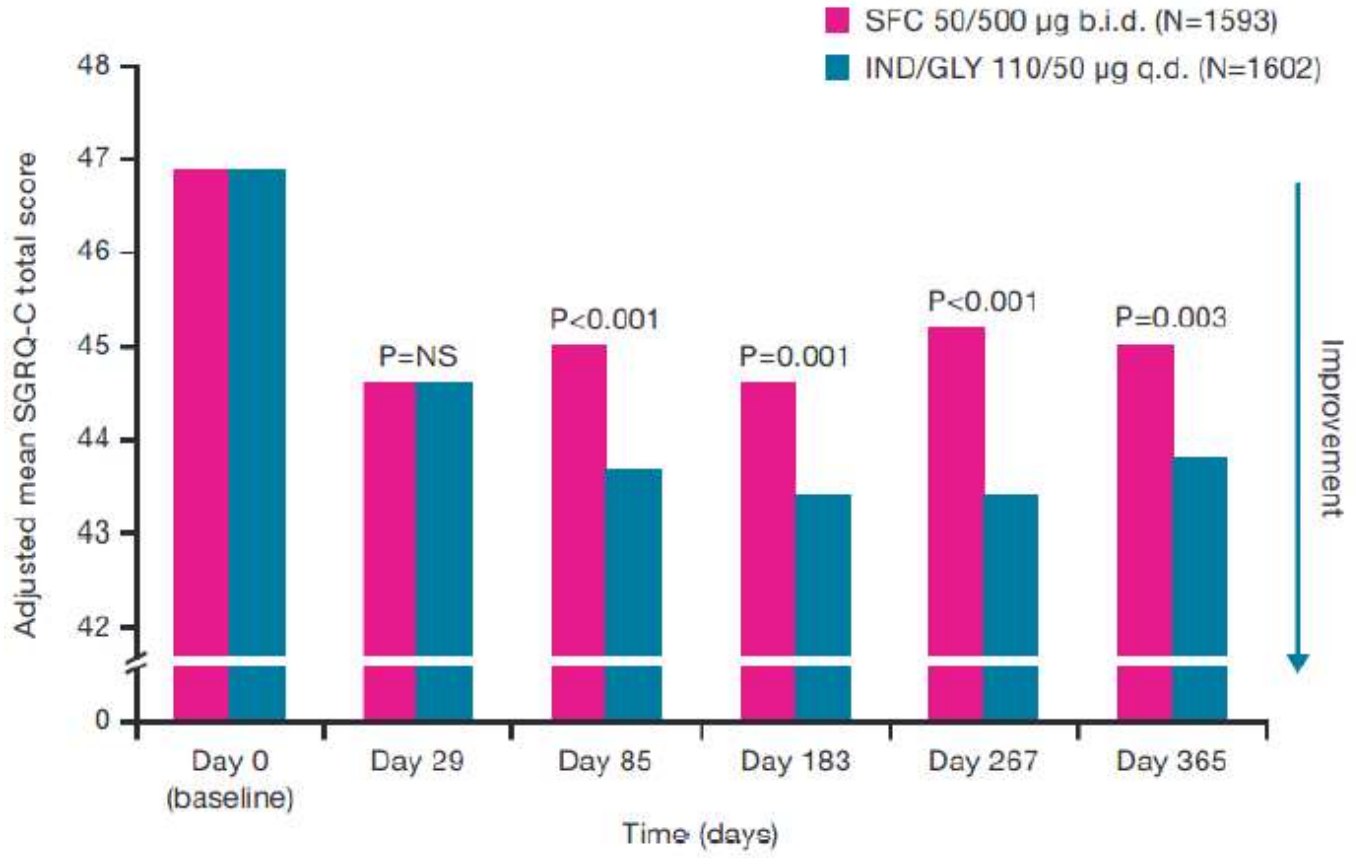
Wedzicha JA, et al. N Engl J Med 2016

IND/GLY significantly improved trough FEV_1 versus SFC at Week 52



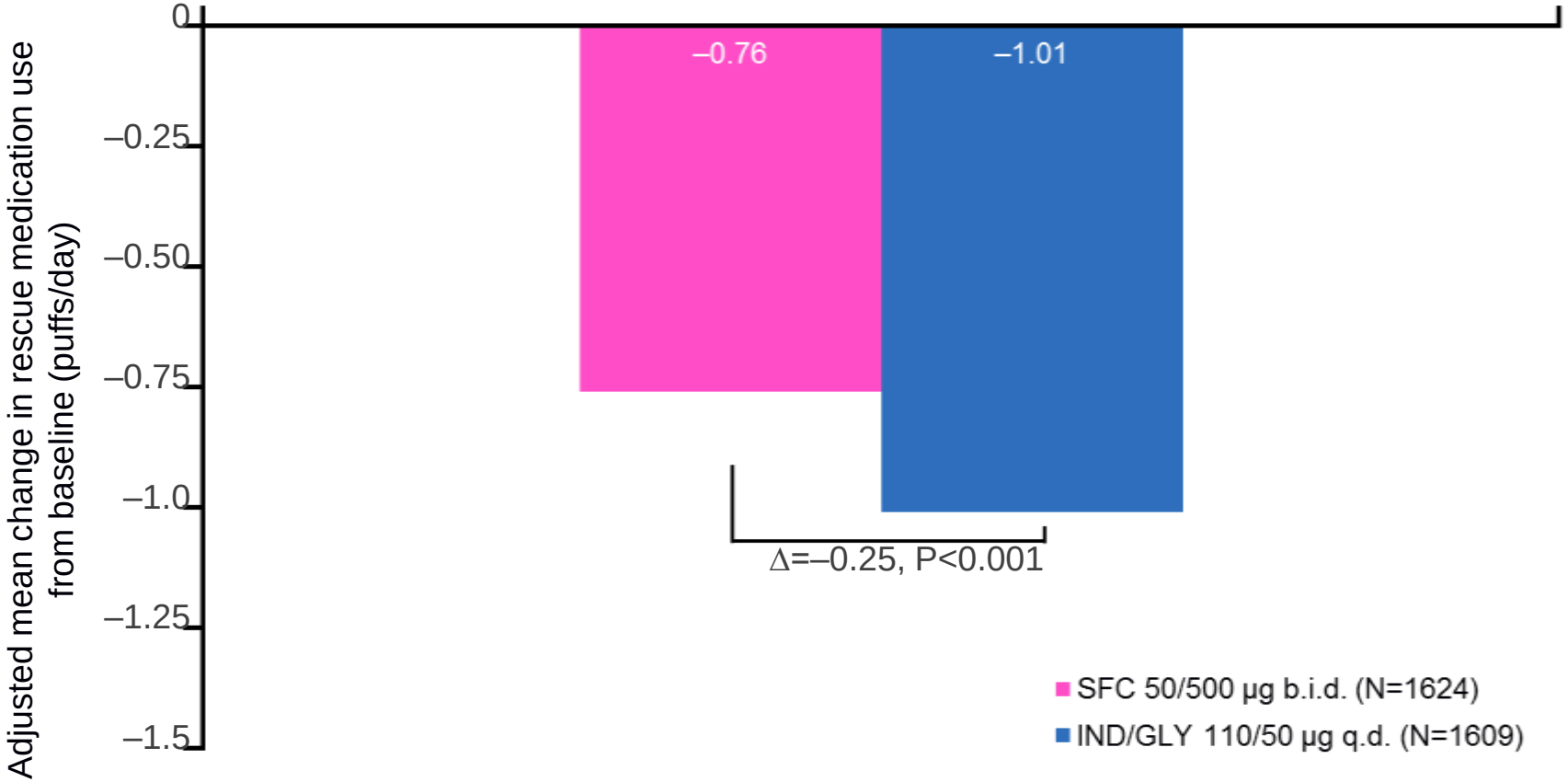
Wedzicha JA, et al. N Engl J Med 2016

IND/GLY significantly improved health status versus SFC at each measured timepoint between Weeks 12 and 52



Wedzicha JA, et al. N Engl J Med 2016

IND/GLY significantly decreased rescue medication use compared with SFC at Week 52



- Baseline rescue medication use was 4 puffs per day, on average, in both treatment groups

Wedzicha JA, et al. N Engl J Med 2016

The incidence of pneumonia was significantly lower with IND/GLY than with SFC

Preferred Term, n (%)	IND/GLY 110/50 µg q.d. (N=1678)	SFC 50/500 µg b.i.d. (N=1680)
Patients with at least one AE	1459 (86.9)	1498 (89.2)
Adverse events ≥3% in any treatment group		
Chronic obstructive pulmonary disease	1299 (77.4)	1374 (81.8)
Nasopharyngitis	197 (11.7)	195 (11.6)
Viral upper respiratory tract infection	132 (7.9)	138 (8.2)
Upper respiratory tract infection bacterial	125 (7.4)	168 (10.0)
Lower respiratory tract infection	82 (4.9)	98 (5.8)
Upper respiratory tract infection	81 (4.8)	83 (4.9)
Pneumonia	53 (3.2)	80 (4.8)
Cough	50 (3.0)	51 (3.0)
Dyspnea	49 (2.9)	51 (3.0)
Influenza	35 (2.1)	56 (3.3)
Oral candidiasis	20 (1.2)	71 (4.2)
SAE(s)	308 (18.4)	334 (19.9)
Death	24 (1.4)	24 (1.4)
Discontinuation due to AE(s)	126 (7.5)	143 (8.5)
Discontinuation due to SAE(s)	85 (5.1)	87 (5.2)
Discontinuation due to non-SAE(s)	49 (2.9)	70 (4.2)

P=0.02

Wedzicha JA, et al. N Engl J Med 2016

Olodaterol+ Tiotropium

- 2 replicate, double-blind, randomized, 12-week studies (ANHELTO 1 and ANHELTO 2); N=2267
- Olodaterol 5 µg OD + tiotropium 18 µg Od vs tiotropium 18 µg OD + placebo
- Moderate to severe COPD
- Primary efficacy end points - FEV1 $AUC_{0–3}$ and trough FEV1 after 12 weeks
- Olodaterol + tiotropium resulted in significant improvements over tiotropium + placebo
  - FEV_1 $AUC_{0–3}$(treatment differences: 0.117 L [*P*<0.001], ANHELTO 1; 0.106 L [*P*<0.001], ANHELTO 2)
  - Trough FEV_1 (treatment differences: 0.062 L [*P*<0.001], ANHELTO 1; 0.040 L [*P*=0.0029], ANHELTO 2)

ZuWallack R et al. Int J Chron Obstruct Pulmon Dis. 2014; 9: 1133–1144.

Vilanterol + Umeclidinium

- 8 RCTs involving 6230 patients
- Significant increases in trough FEV1 and FVC when compared with mono-components
- Beneficial effects on dyspnea, albuterol use, and HRQoL compared with the other three groups
- No increase in adverse effects

Wang L . Clin Drug Investig. 2016 Nov;36(11):865-875.

Vilanterol+Fluticasone

- Double-blind randomised controlled trial (SUMMIT) done in 1368 centres in 43 countries
- Randomly assigned (1:1:1:1) - once daily inhaled placebo, fluticasone furoate (100 µg), vilanterol (25 µg), or the combination of fluticasone furoate (100 µg) and vilanterol (25 µg)
- 16 590 were randomised; 16 485 patients were included in the ITT analysis
- Primary outcome – All-cause mortality unaffected
- Rate of decline in FEV1 was reduced by
  - combination therapy (38 mL per year [SE 2·4] vs 46 mL per year [2·5] for placebo, difference 8 mL per year [95% CI 1-15])
  - fluticasone furoate (difference 8 mL per year [95% CI 1-14])
  - vilanterol (difference -2 mL per year [95% CI -8 to 5])

Vestbo J, et al. Lancet. 2016 Apr 30;387(10030):1817-26

Coming soon…

- Once daily, single dose- triple therapy for COPD
- IMPACT Trial
- Fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI) *versus* FF/VI or UMEC/VI over a 52-week treatment period
- Co-primary endpoints: the annual rate of on-treatment moderate and severe exacerbations

Pascoe SJ et al. Eur Respir J 2016; 48: 320–330

Take home message

- Once-daily dosing has the potential to improve medication adherence
- 24-h activity is also likely to improve nocturnal and early morning symptoms
- Pharmacological stenting with ultra LABA+LAMA
- No major differences between individual drugs
- Triple therapy and MABA awaited