천식연구회 **COPD** 연구회 공동 심포지움

1st line treatment in each COPD groups

2014년2월15일
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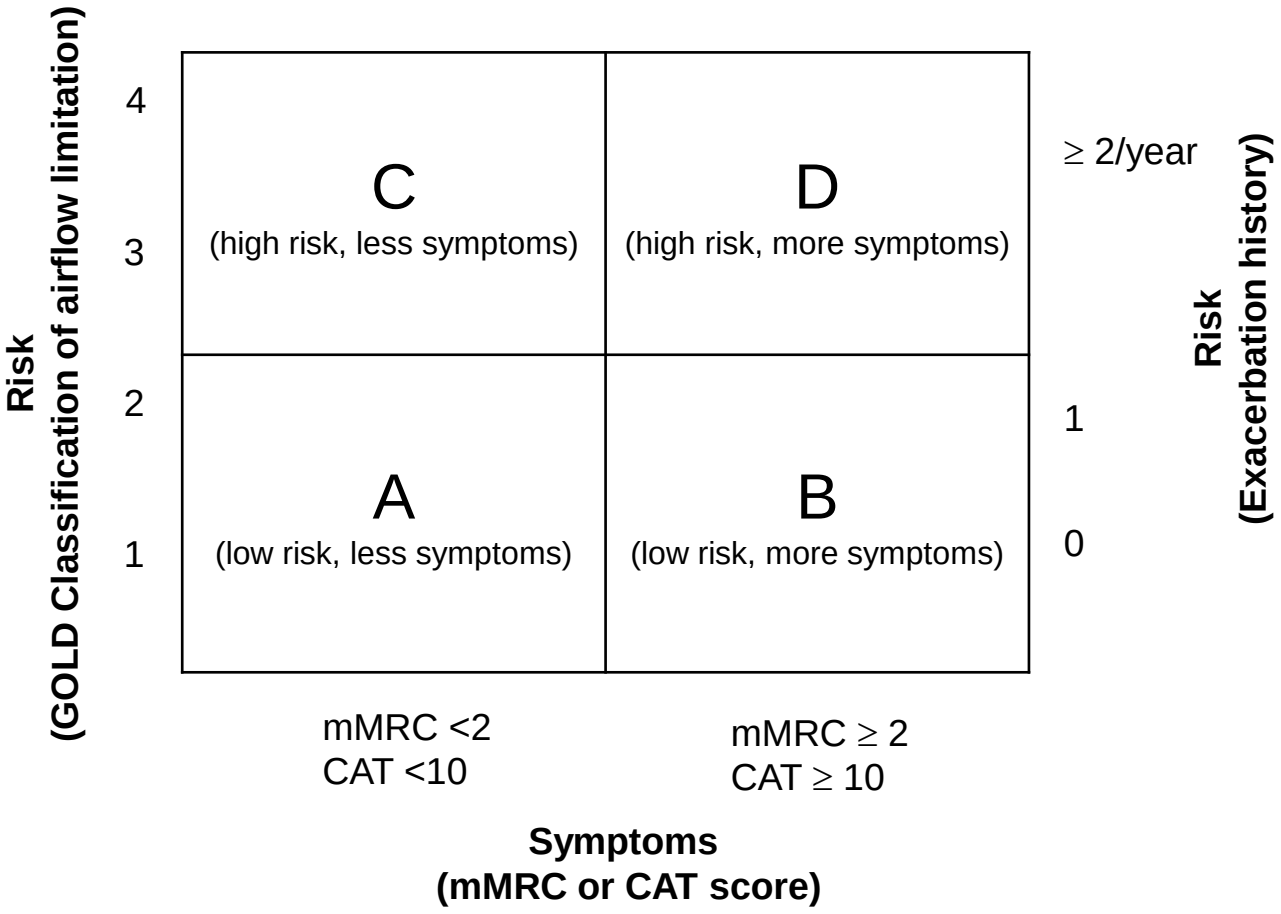
Combined COPD Assessment



GOLD 2014

Initial pharmacologic management

Group	Recommended First choice	Alternatives choices	Other possible treatments*
A	SAMA prn or SABA prn	LAMA or LABA or SABA + SAMA	Theophylline
B	LAMA or LABA	LABA + LAMA	SABA ± SAMA Theophylline
C	ICS+LABA or LAMA	LABA + LAMA or LAMA + PDE4 inhibitor or LABA + PDE4 inhibitor	SABA ± SAMA Theophylline
D	ICS+ LABA and/or LAMA	ICS + LAMA + LABA or ICS+LABA + PDE4 inhibitor or LAMA + PDE4 inhibitor or LAMA + LABA	Carbocysteine SABA ± SAMA Theophylline

*medications in this column can be used alone or in combination with other options in the recommneded first choice and alternative choice column

First and alternative choices

	A	B	C	D
SAMA prn *or* SABA prn	First			
SABA + SAMA	Alternative			
LABA	Alternative	First		
LAMA	Alternative	First	First	First
LABA + LAMA		Alternative	Alternative	Alternative
ICS+LABA			First	First
LAMA + PDE4i			Alternative	Alternative
LABA + PDE4i			Alternative	
ICS+LABA+LAMA				Alternative
ICS+LABA+PDE4i				Alternative

LAMA vs. LABA for GOLD B

Tiotropium vs. LABA

	Duration	N	LABA	Inclusion criteria	Mean FEV1	Primary outcome
Briggs 2005	12 wk	653	salmeterol	FEV1≤60%	37.7%	FEV1
Brusasco 2003	6 mo	1207	Salmeterol	FEV1≤65%	39.2%	Exacerbation, health resource use, dyspnea, QoL, PFT
Burl 2011	12 wk	1598	Indacaterol	FEV1≤80%	54.3%	FEV1
Donohue 2010	26 wk	1683	Indacaterol	30%<FEV1<80%	56%	FEV1
Vogelmeier 2008	6 mo	847	Formoterol	FEV1≤70%	51.6%	FEV1
Vogelmeier 2011	12 mo	7384	Salmeterol	FEV1≤70% and ≥ 1 exacerbation within previous yr	49.2%	Time to first exacerbation

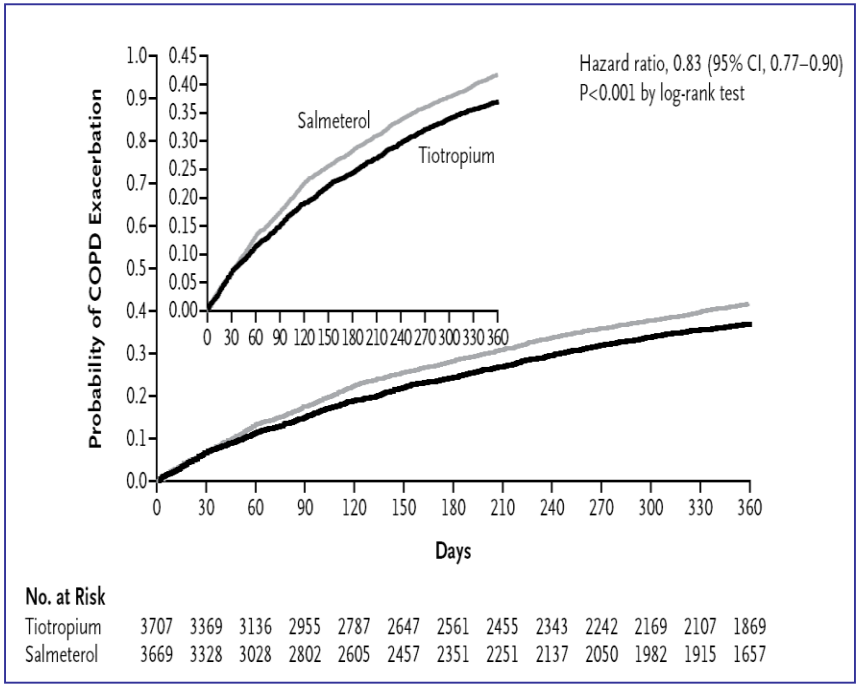
Cochrane review 2013

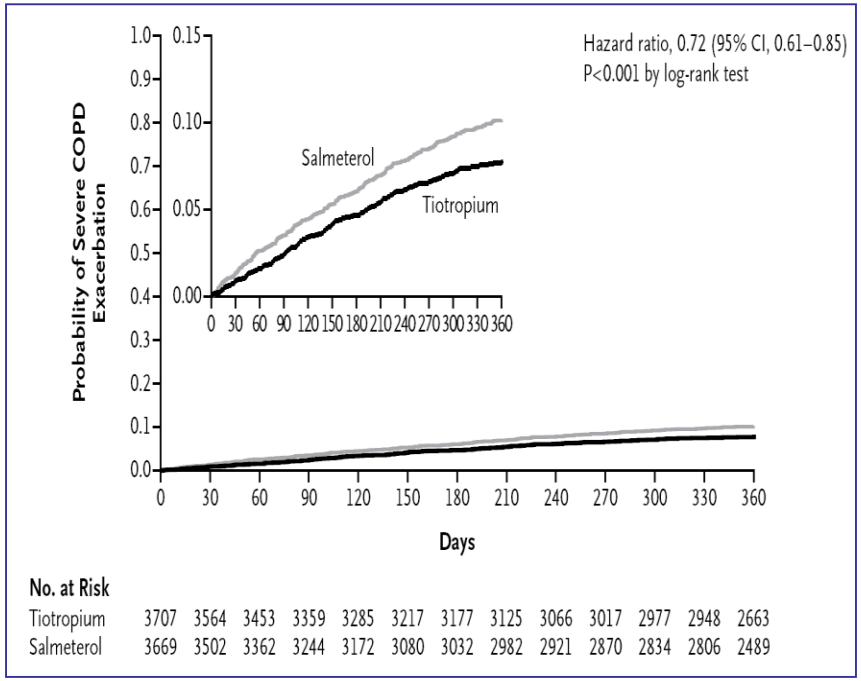
Tiotropium versus Salmeterol for the Prevention of Exacerbations of COPD

- 1-year, randomized, double-blind, double-dummy, parallel-group trial
- moderate-to-very-severe COPD and a history of exacerbations in the preceding year
- N=7,376, mean FEV1 = 49.2%/49.4% of predicted
  - GOLD II **47.8%/49.6%,** GOLD III 43.1%/42.1%, GOLD IV 8.9%/7.9%
- Allowed ICS (used in 53.6% and 53.3% of each group)
- Tiotropium 18 µg qd vs. salmeterol 50 µg bid
- Primary end point : the time to the first exacerbation of COPD

POET-COPD study.N Engl J Med 2011;364:1093-103

Tiotropium increased the time to the first exacerbation c/w salmeterol

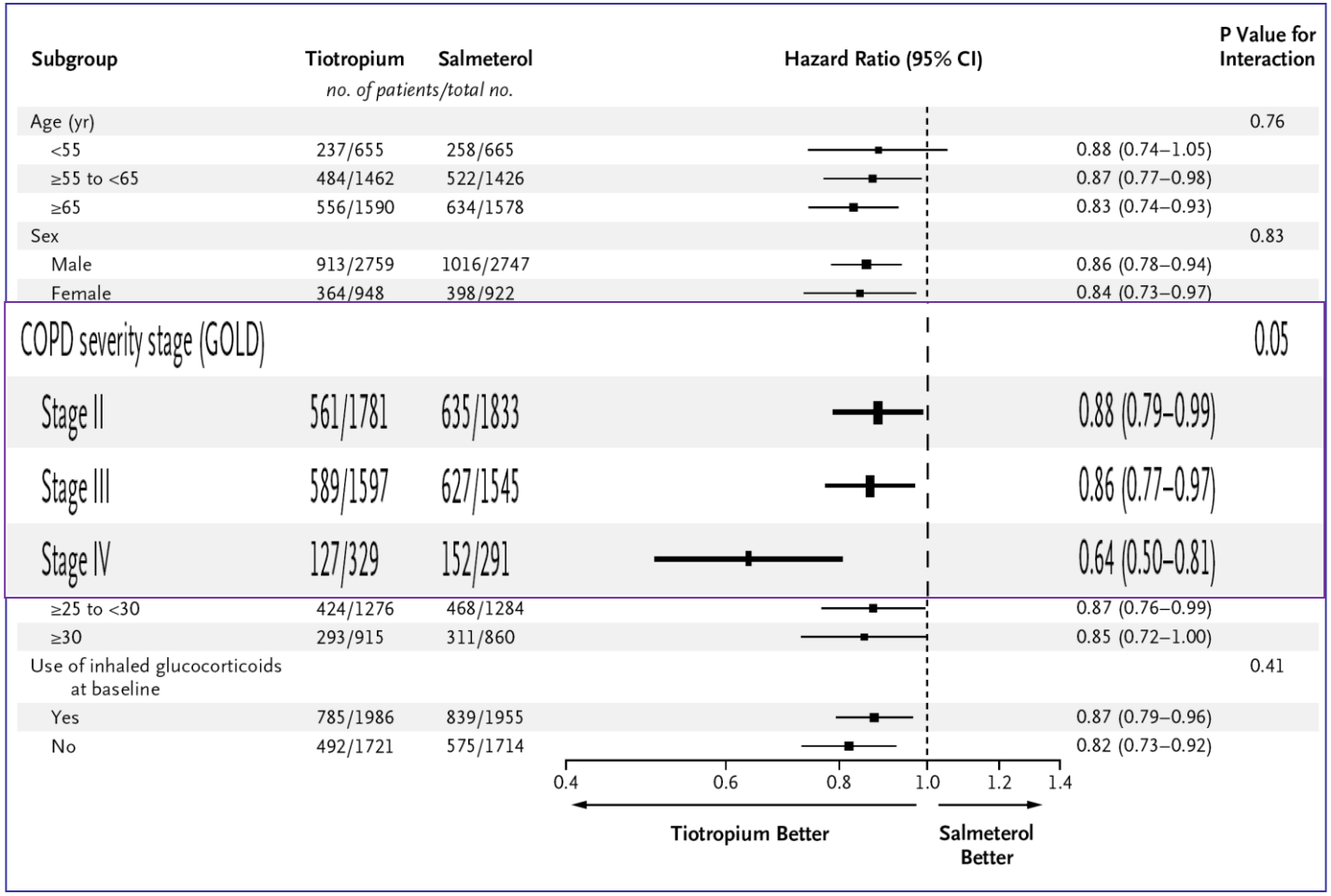




187 days vs. 145 days (HR 0.83)

POET-COPD study.N Engl J Med 2011;364:1093-103

Tiotropium vs. salmeterol -exacerbation, subgroup analysis-



POET-COPD study.N Engl J Med 2011;364:1093-103

Blinded 12-week comparison of once-daily indacaterol and tiotropium in COPD

- 12 weeks, randomized, blinded, parallel group, double-dummy trial
- moderate-to-severe COPD
- N=1,683, mean FEV1 = 56% of predicted
- Allowed ICS (used in 38.2~39.5%)
- Indacaterol 150ug qd vs. Tiotropium 18 μg qd
- Objectives: non-inferiority of indacaterol to tiotropiumin their effect on ‘‘trough’’ FEV1

INTENSITY study. Eur Respir J 2011; 38: 797–803

Demographics and baseline characteristics

	Indacaterol	Tiotropium
Subjects n	794	799
Age yrs	63.6±8.60	63.4±8.29
Male/female	70/30	67/33
Duration of COPD yrs	7.0±6.01	7.0±6.32
ICS use	54	56
Ex-smoker/smoker	55/45	56/44
Smoking history pack-yrs	43.2±20.87	41.8±19.81
FEV_1 post-bronchodilator L	1.53±0.459	1.52±0.447
FEV_1 reversibility	14.1±12.63	13.7±13.44
FEV_1 % pred post-bronchodilator	54.6±12.80	54.3±12.81
FEV_1/FVC post-bronchodilator	51.0±9.38	51.2±9.42
Use of as-needed salbutamol puffs·day^{-1}	3. 8±3.74	3.6±3.51
BDI score	6.8±2.2	6.8±2.23
SGRQ score	42.3±17.60	42.7±18.04

INTENSITY study. Eur Respir J 2011; 38: 797–803

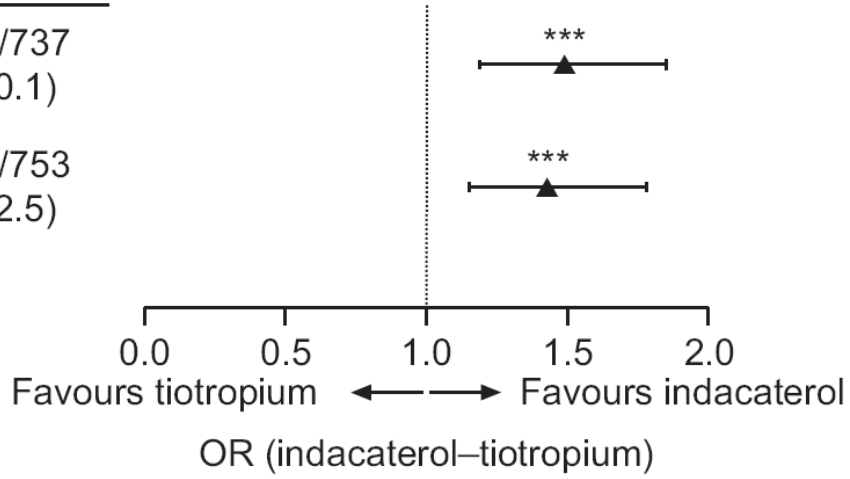
Trough FEV1 at week 12

	Indacaterol	Tiotropium	Indacaterol–tiotropium difference	p-value for non-inferiority	p-value for superiority
All patients	1.44±0.010	1.43±0.010	0.00 (-0.02–0.02)	<0.001	0.850
Sex					
Male	1.44±0.010	1.44±0.010	0.00 (-0.02–0.02)	<0.001	0.987
Female	1.44±0.015	1.43±0.014	0.01 (-0.03–0.04)	<0.001	0.659
Smoking status					
Ex-smoker	1.45±0.011	1.46±0.011	-0.01 (-0.04–0.01)	<0.001	0.409
Current smoker	1.44±0.012	1.42±0.012	0.02 (-0.01–0.05)	<0.001	0.177
COPD severity					
Moderate or less	1.45±0.011	1.42±0.011	0.03 (0.01–0.05)	<0.001	0.013
Severe or very severe	1.42±0.014	1.47±0.013	-0.04 (-0.07– -0.01)	0.215	0.007
ICS use					
No	1.46±0.012	1.44±0.012	0.02 (-0.01–0.04)	<0.001	0.244
Yes	1.43±0.011	1.44±0.011	-0.01 (-0.03–0.02)	<0.001	0.495
Reversibility to salbutamol					
⩽12%	1.43±0.012	1.42±0.012	0.01 (-0.02–0.03)	<0.001	0.631
>12%	1.46±0.013	1.46±0.013	0.00 (-0.03–0.03)	<0.001	0.948

INTENSITY study. Eur Respir J 2011; 38: 797–803

Proportions of patients with or exceeding the MCID for TDI and SGRQ score

	Indacaterol n/N (%)	Tiotropium n/N (%)
TDI score ≥1	422/729 (57.9)	369/737 (50.1)
SGRQ score ≥4	375/743 (50.5)	320/753 (42.5)



OR 1.49 (95% CI 1.19–1.85)

OR 1.43 (95% CI 1.15–1.78)

INTENSITY study. Eur Respir J 2011; 38: 797–803

Once-Daily Bronchodilators for Chronic Obstructive Pulmonary Disease

Indacaterol Versus Tiotropium

- 26 weeks, randomized, partly-blind , partly placebo-controlled, parallel group trial
- moderate-to-severe COPD
- N=1,683, mean FEV1 = 56% of predicted
- Allowed ICS (used in 38.2~39.5%)
- Indacaterol 150ug qd vs. 300ug qd vs. Tiotropium 18 μg qd vs placebo
- Objectives:
  - To demonstrate greater efficacy of indacaterol vs. placebo on FEV1 at 24 hours post dose (trough) after 12 weeks
  - To compare efficacy with placebo and tiotropium
  - To evaluate safety and tolerability over 26 weeks.

INHANCE study. Am J Respir Crit Care Med 2010;182:155-162

Differences between active and placebo treatment in effect on trough FEV1

	Least Squares Mean ± SE (L) Placebo	Treatment Difference Vs Placebo (L): Least Squares Mean and 95% CI*		
		Indacaterol 150 μg	Indacaterol 300 μg	Tiotropium
Day 2	1.34 (0.011)	0.11 (0.08, 0.13)	0.14 (0.12, 0.16)‡	0.10 (0.07, 0.12)
n	391	400	396	395
Week 2	1.29 (0.013)	0.17 (0.14, 0.20)†	0.18 (0.15, 0.21)‡	0.14 (0.11, 0.17)
n	377	389	391	393
Week 12	1.28 (0.015)	0.18 (0.14, 0.22)‡	0.18 (0.14, 0.22)‡	0.14 (0.10, 0.18)
n	376	389	389	393
Week 26	1.26 (0.017)	0.16 (0.12, 0.19)	0.18 (0.14, 0.22)†	0.14 (0.10, 0.18)
n	317	349	361	356

Definition of abbreviation: CI = confidence interval.

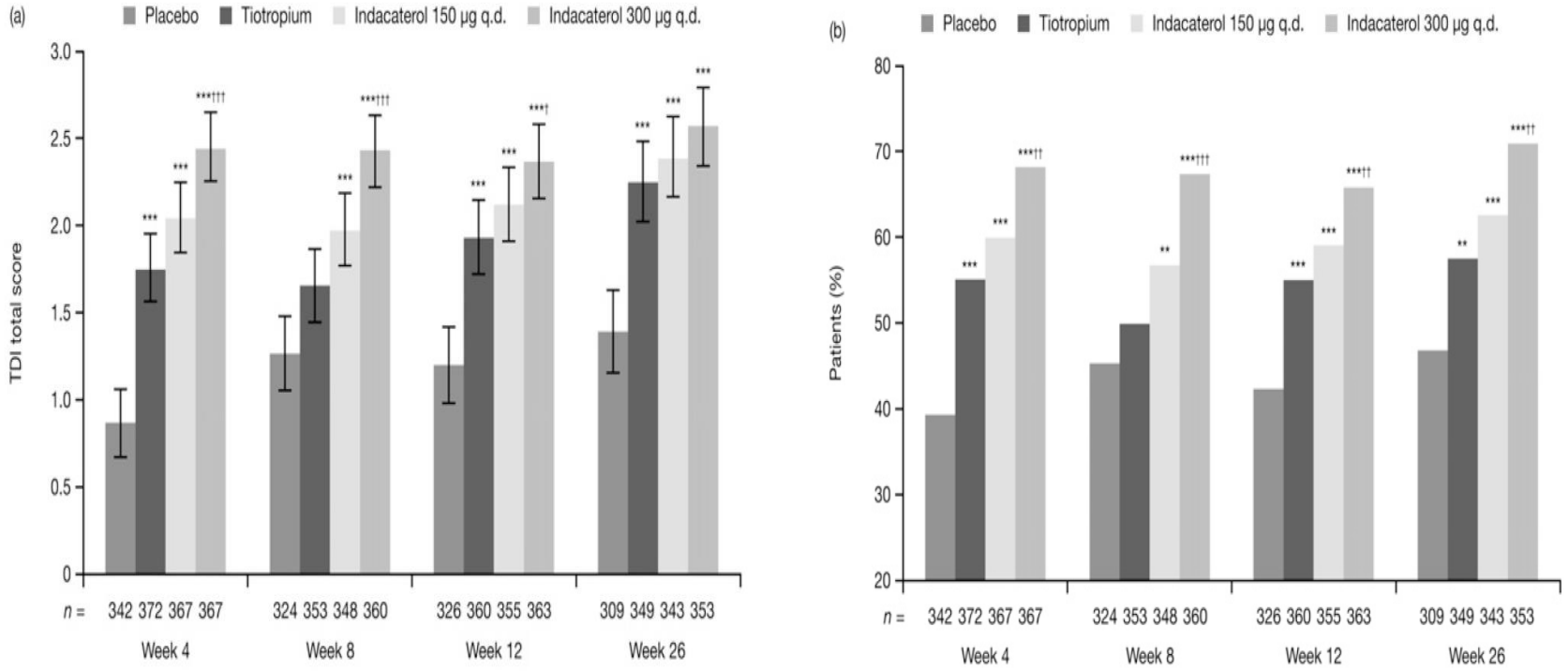
* Week 12 CIs are 98.75%. All treatment differences versus placebo significant for superiority at $P < 0.001$. Both indacaterol doses significant for noninferiority versus tiotropium at $P < 0.001$.

† $P < 0.05$.

‡ $P \leq 0.01$ for superiority comparison versus tiotropium.

INHANCE study. Am J Respir Crit Care Med 2010;182:155-162

TDI total score and the proportions of patients with MCID from baseline



**P< 0.01 and ***P <0.001 versus placebo; †P< 0.05, ††P ≤ 0.01, and †††P< 0.001 versus tiotropium.

INHANCE study. Am J Respir Crit Care Med 2010;182:155-162

Health status assessment by SGRQ score at week 26

	Least Squares Mean (SE)	Treatment Difference Vs. Placebo: Least Squares Mean (95% CI)		
	Placebo	Indacaterol 150 µg	Indacaterol 300 µg	Tiotropium
n	346	346	360	357
Total score	40.4 (0.79)	−3.3 (−5.1 to −1.5)*†	−2.4 (−4.2 to −0.6)‡	−1.0 (−2.8 to 0.8)
Symptoms component	49.0 (1.18)	−4.0 (−6.8 to −1.3)‡§	−4.3 (−7.0 to −1.6)‡§	−1.3 (−4.0 to 1.5)
Activity component	56.7 (1.01)	−4.8 (−7.1 to −2.5)*§	−3.1 (−5.3 to −0.8)‡	−2.2 (−4.5 to 0.1)
Impacts component	27.8 (0.85)	−2.3 (−4.3 to −0.3)‖§	−1.5 (−3.5 to 0.4)	−0.2 (−2.2 to 1.8)

* p<0.001 vs. placebo,† p ≤ 0.01 vs. tiotropium, ‡ p<0.01 vs. placebo, § p<0.01 vs. Tiotropium, ‖ p<0.05 vs. placebo

INHANCE study. Am J Respir Crit Care Med 2010;182:155-162

LAMA+LABA vs. LABA or LAMA for GOLD B,C,D

Tiotropium + LABA vs. Tiotropium

	Duration	N	LABA	Inclusion criteria	Mean FEV1	Primary outcome
Aaron 2007	12 mo	304	Salmeterol	FEV1≤65% and ≥ 1 exacerbation within previous yr	38%	Proportion of patients with one or more AECOPD
Mahler 2010a	12 wk	1134	Indacaterol	30%≤FEV1≤65%	49%	FEV1
Mahler 2010b	12 wk	1142	Indacaterol	30%≤FEV1≤65%	49%	FEV1
Tashkin 2009	12 wk	255	Formoterol	30%<FEV1<70%		FEV1
Vogelmeier 2008	6 mo	638	Formoterol	FEV1≤70%	52.6%	FEV1

Cochrane review 2012

LABA + Tiotropium vs. Tiotropium for COPD

Outcomes	Illustrative comparative risks (95%CI)		Relative effect (95%CI)	No of participants
	Assumed risk	Corresponding risk		
	Tio	Tio+LABA		
Change in QoL (SGRQ)	Mean change : -4.5unit	Mean change : -6.3unit (-7.43to-4.79)	MD -1.61 (-2.93 to -0.29)	732
Hospital admission (exacerbation	88/1000	93/1000 (57 to 148)	OR 1.07 (0.63 to1.81)	732
Hospital admission (all cause)	119/1000	120/1000 (79 to 179)	OR 1.01 (0.63 to 1.61)	732
Mortality (all cause)	4/1000	6/1000 (2 to 16)	OR 1.56 (0.56 to 4.33)	3263

Cochrane review 2012

Concurrent use of indacaterol plus tiotropium in patients with COPD provides superior bronchodilation compared with tiotropium alone: a randomised, double-blind comparison

- 12 weeks, two identically designed, randomised, double-blind studies
- 30%≤FEV1 ≤ 65%
- N= 1,134 and 1,142. mean FEV1 = 48.3~48.9%
- Indacaterol + tiotropium vs. tiotropium
- Primary objective : superiority of indacaterol plus tiotropium versus tiotropium plus placebo in its effect on standardised area under the curve of FEV1 from 5 min to 8 h post dose after 12 weeks

INTRUST-1,2 study. Thorax 2012;67:781-788

Demographics and baseline characteristics

	Study 1		Study 2	
	Indacaterol + tiotropium (n=570)	Tiotropium + placebo (n=561)	Indacaterol + tiotropium (n=572)	Tiotropium + placebo (n=570)
Age (years), mean (SD)	64.0 (9.07)	63.4 (9.22)	63.1 (8.83)	62.8 (8.98)
Sex, men/women, %	70/30	67/33	63/37	68/32
Race, %				
Caucasian	78.2	76.8	77.8	79.3
Black	1.1	3.0	3.0	1.9
Asian	5.4	4.5	16.6	16.5
Native American	0.4	1.2	—	—
Severity of COPD, n (%)*				
Moderate†	47	47	46	46
Severe or very severe	53	53	54	54
ICS use, yes/no %	52/48	52/48	57/43	51/49
FEV_1/FVC (post salbutamol)	46.4 (9.74)	45.8 (10.00)	47.0 (10.21)	47.2 (9.53)
FEV_1, litres (pre salbutamol), mean (SD)	1.15 (0.357)	1.15 (0.384)	1.14 (0.364)	1.15 (0.356)
FEV_1, litres (post-salbutamol), mean (SD)	1.32 (0.367)	1.33 (0.418)	1.29 (0.368)	1.32 (0.374)
FEV_1 reversibility‡ (pre/post salbutamol), %	16.5 (14.48)	17.3 (17.13)	16.3 (15.85)	16.5 (16.27)
FEV_1, litres (pre ipratropium), mean (SD)	1.16 (0.367)	1.17 (0.396)	1.16 (0.373)	1.18 (0.373)
FEV_1, litres (post ipratropium), mean (SD)	1.36 (0.419)	1.35 (0.429)	1.33 (0.402)	1.35 (0.407)
FEV_1 reversibility‡ (pre/post ipratropium), %	18.5 (15.68)	16.6 (14.10)	16.4 (15.32)	16.5 (15.20)

INTRUST-1,2 study. Thorax 2012;67:781-788

Differences between treatments (indacaterol plus tiotropiume -tiotropium)

• Superiority of indacaterol plus tiotropium versus tiotropium plus placebo was demonstrated for FEV1 $AUC_{5mine-8h}$ at week 12, with differences of 130 ml (95% CI 100 to 150) and 120 ml (95% CI 90 to 140) in studies 1 and 2, respectively (both p<0.001).

	Differences between indacaterol + tiotropium versus tiotropium + placebo			
	FEV_1 $AUC_{5min-8h}$		Trough FEV_1	
	Study 1	Study 2	Study 1	Study 2
COPD severity†				
Moderate‡	120 ml (90 to 160) (n=233/237)§	130 ml (90 to 160) (n=247/237)	90 ml (50 to 130) (n=259/260)	90 ml (60 to 120) (n=261/258)
Severe or very severe	130 ml (100 to 160) (n=272/267)	110 ml (80 to 140) (n=283/267)	70 ml (30 to 110) (n=302/289)	60 ml (30 to 90) (n=304/306)
Smoking status				
Ex-smoker	120 ml (90 to 150) (n=300/324)	140 ml (110 to 170) (n=331/285)	70 ml (40 to 110) (n=335/350)	80 ml (60 to 110) (n=352/322)
Current smoker	130 ml (90 to 170) (n=205/180)	90 ml (50 to 120) (n=199/219)	80 ml (40 to 130) (n=226/199)	60 ml (20 to 90) (n=213/242)
ICS use				
ICS non-users	120 ml (90 to 160) (n=242/236)	140 ml (100 to 170) (n=229/251)	70 ml (30 to 110) (n=271/260)	90 ml (60 to 120) (n=244/274)
ICS users	130 ml (100 to 160) (n=263/268)	100 ml (70 to 140) (n=301/253)	80 ml (50 to 120) (n=290/289)	60 ml (30 to 90) (n=321/290)

INTRUST-1,2 study. Thorax 2012;67:781-788

Patient-reported symptoms and use of as-needed salbutamol over 12 weeks

	Study 1		Study 2	
	Indacaterol + tiotropium	Tiotropium + placebo	Indacaterol + tiotropium	Tiotropium + placebo
Baseline* symptom score†				
Full 24 h	11.9 (5.98)	10.8 (5.77)	11.6 (5.91)	11.7 (5.42)
Daytime	6.2 (2.97)	5.7 (2.90)	6.1 (2.94)	6.1 (2.71)
Night-time	5.6 (3.16)	5.2 (3.03)	5.5 (3.06)	5.5 (2.86)
Change from baseline symptom score (full 24 h) during treatment	−2.1 (0.20)	−1.6 (0.21)	−2.2 (0.21)	−1.5 (0.21)
Difference between treatments	−0.5 (−0.9 to −0.08)		−0.6 (−1.1 to −0.2)	
Change from baseline symptom score (daytime) during treatment	−1.2 (0.10)	−0.9 (0.10)	−1.1 (0.12)	−0.8 (0.12)
Difference between treatments	−0.3 (−0.5 to −0.06)		−0.4 (−0.6 to −0.1)	
Change from baseline symptom score (night-time) during treatment	−1.0 (0.10)	−0.8 (0.10)	−1.0 (0.12)	−0.7 (0.12)
Difference between treatments	−0.2 (−0.4 to −0.03)		−0.3 (−0.5 to −0.1)	
Baseline† salbutamol use (puffs/day)	5.5 (4.24) (n=538)	5.0 (4.45) (n=538)	4.9 (3.91) (n=555)	4.5 (3.97) (n=543)
Change from baseline salbutamol use during treatment (puffs/day)	−2.5 (0.17)	−1.3 (0.17)	−2.1 (0.17)	−1.4 (0.17)
Difference between treatments	−1.1 (−0.8 to −1.5)		−0.7 (−1.0 to −0.4)	
Days during baseline† with no salbutamol use (%)	16.1 (30.95) (n=532)	21.9 (35.35) (n=521)	14.4 (28.64) (n=545)	19.3 (32.55) (n=536)
Days during treatment with no salbutamol use (%)	43.2 (1.91)	34.2 (1.93)	38.7 (1.94)	33.6 (1.92)
Difference between treatments	9.0 (5.1 to 12.8)		5.1 (1.4 to 8.8)	

INTRUST-1,2 study. Thorax 2012;67:781-788

Dual bronchodilation with QVA149 *versus* single bronchodilator therapy: the SHINE study

- 26 weeks, multicentre, randomised, double-blind, placebo- and active-controlled
- moderate-to severe COPD
- N=2144, mean FEV1= 54.9~55.7% predicted
- once-daily QVA149, indacaterol 150 mg, glycopyrronium 50 mg, open-label tiotropium 18 mg or placebo.
- Primary end-point ： trough FEV1 at week 26 for QVA149 versus its mono-components

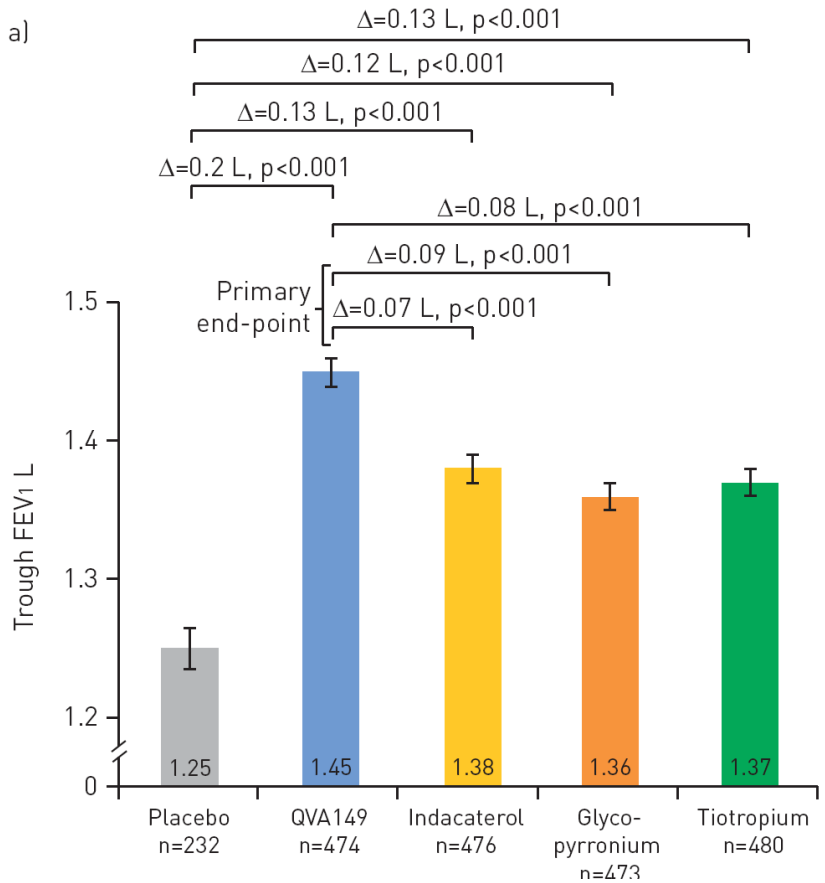
SHINE study. Eur Respir J 2013; 42: 1484-1494

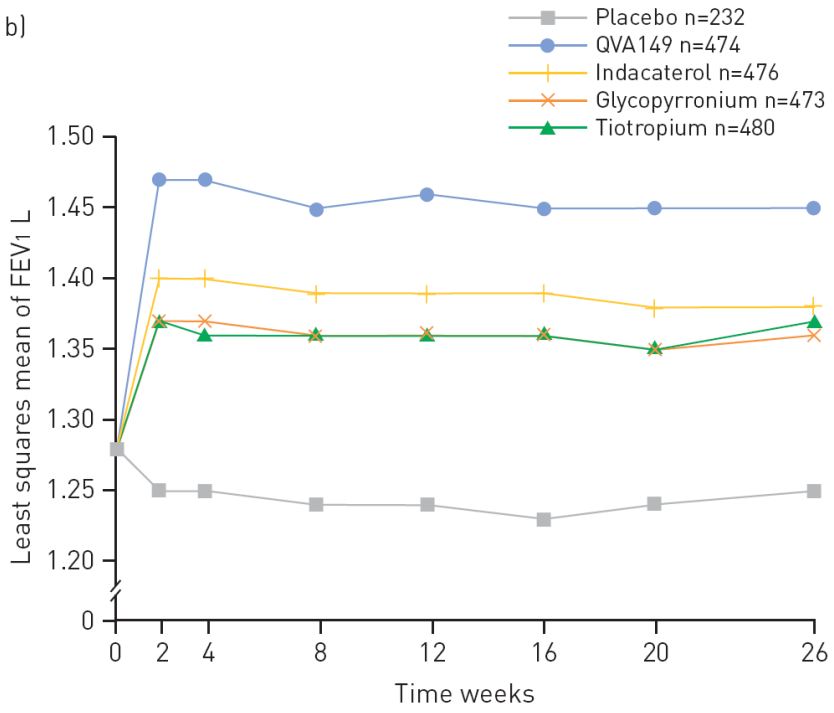
Demographics and baseline characteristics

	Placebo	QVA149 110/50 µg	Indacaterol 150 µg	Glycopyrronium 50 µg	Tiotropium 18 µg
Subjects n	232	474	476	473	480
Age years	64.4±8.6	64.0±8.9	63.6±8.8	64.3±9.0	63.5±8.7
Male	169 (72.8)	362 (76.4)	354 (74.4)	365 (77.2)	360 (75.0)
Race					
Caucasian	155 (66.8)	321 (67.7)	332 (69.7)	315 (66.6)	322 (67.1)
Asian	71 (30.6)	140 (29.5)	131 (27.5)	137 (29.0)	135 (28.1)
Other	6 (2.6)	13 (2.7)	13 (2.7)	21 (4.4)	23 (4.8)
Duration of COPD years	6.4±5.7	6.0±5.5	6.3±5.6	6.5±5.8	6.1±5.5
COPD severity					
Moderate	157 (67.7)	313 (66.0)	294 (61.8)	298 (63.0)	296 (61.7)
Severe	75 (32.3)	161 (34.0)	182 (38.2)	173 (36.6)	184 (38.3)
ICS use	134 (57.8)	268 (56.5)	269 (56.5)	274 (57.9)	282 (58.8)
Smoking status					
Ex-smoker	139 (59.9)	282 (59.5)	292 (61.3)	284 (60.0)	291 (60.6)
Current smoker	93 (40.1)	192 (40.5)	184 (38.7)	189 (40.0)	189 (39.4)
COPD exacerbation history#					
0	184 (79.3)	352 (74.3)	348 (73.1)	346 (73.2)	363 (75.6)
1	37 (15.9)	94 (19.8)	106 (22.3)	91 (19.2)	93 (19.4)
⩾2	11 (4.7)	28 (5.9)	22 (4.6)	36 (7.6)	24 (5.0)
Pre-bronchodilator FEV_1 L	1.3±0.5	1.3±0.5	1.3±0.5	1.3±0.5	1.3±0.5
Post-bronchodilator FEV_1 L	1.5±0.5	1.5±0.5	1.5±0.5	1.5±0.5	1.5±0.5
Post-bronchodilator FEV_1 % pred	55.2±12.7	55.7±13.2	54.9±12.9	55.1±13.4	55.1±13.5
Post-bronchodilator FEV_1 reversibility %	19.3±15.9	20.4±16.8	20.5±16.8	20.0±17.6	20.6±17.5
Post-bronchodilator FEV_1/FVC %	48.6±10.4	49.1±10.1	48.4±10.6	48.2±10.9	49.2±10.8

SHINE study. Eur Respir J 2013; 42: 1484-1494

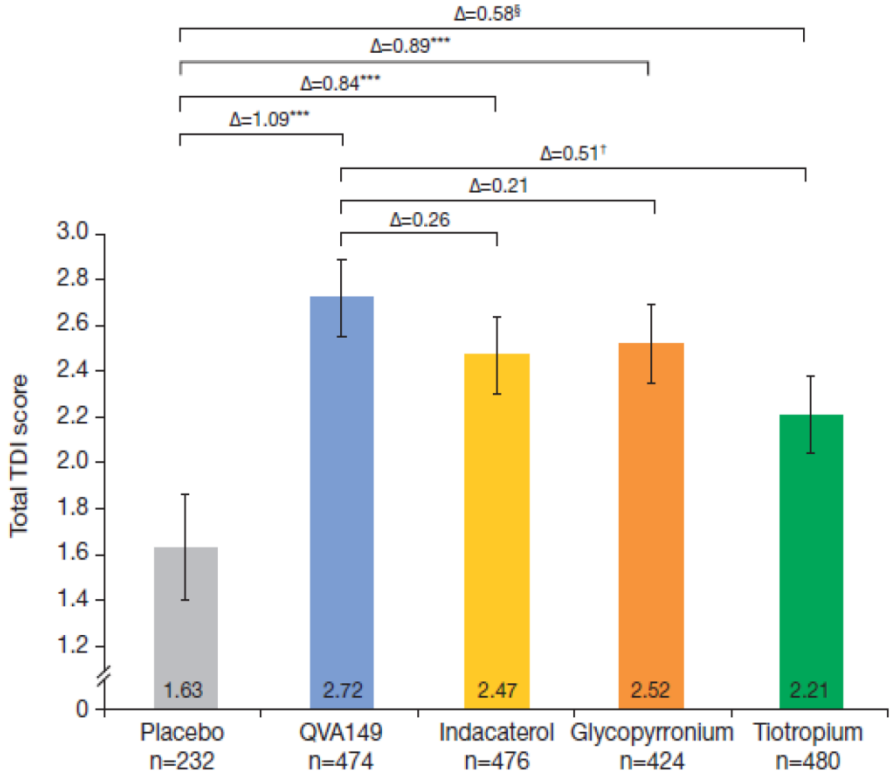
QVA149 provided superior improvements in lung function

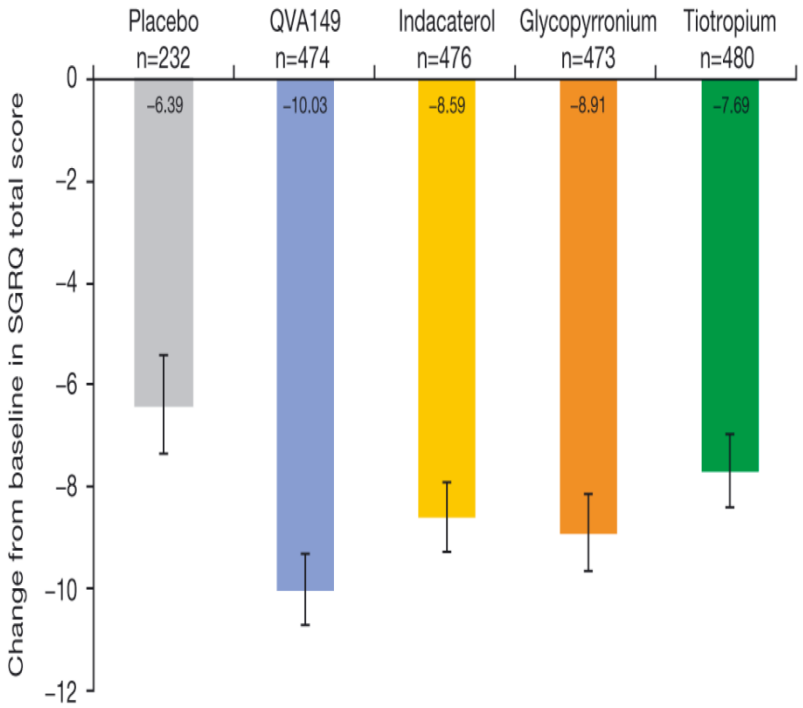




SHINE study. Eur Respir J 2013; 42: 1484-1494

QVA149 significantly improved dyspnoea and health status versus placebo and tiotropium at week 26





SHINE study. Eur Respir J 2013; 42: 1484-1494

Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study

- 64 weeks, multicentre, parallel-group study
- GOLD III-IV and ≥ 1 moderate COPD exacerbation in the past year
- N= 2,224 , mean FEV1 predicted : 37.0%/37.3%/37.4%
- once-daily QVA149 vs. glycopyrronium 50 µg vs. tiotropium 18
- Primary objective : superiority of QVA149 for the rate of moderate or severe COPD exacerbations c/w glycopyrronium.
- Key secondary objective : superiority of QVA149 for the rate of moderate to severe COPD exacerbations c/w titotropum

SPARK study. Lancet Respir Med 2013;1:199-209

Baseline characteristics

	QVA149 (n=729)	Glycopyrronium (n=740)	Tiotropium (n=737)
Age (years)	63·1 (8·1)	63·1 (8·0)	63·6 (7·8)
Men	556 (76%)	542 (73%)	553 (75%)
Race			
White	594 (81%)	605 (82%)	613 (83%)
Asian	89 (12%)	92 (12%)	79 (11%)
Black	4 (1%)	5 (1%)	7 (1%)
Other	42 (6%)	38 (5%)	38 (5%)
Severity of airflow limitation			
Severe*	578 (79%)	584 (79%)	581 (79%)
Very severe	150 (21%)	155 (21%)	156 (21%)
Duration of COPD (years)	7·2 (5·8)	7·1 (5·3)	7·2 (5·5)
Number of COPD exacerbations in previous year			
0	8 (1%)	13 (2%)	11 (1%)
1	557 (76%)	572 (77%)	552 (75%)
≥2	164 (22%)	155 (21%)	174 (24%)
Inhaled corticosteroid use at baseline	546 (75%)	557 (75%)	559 (76%)
Current smoker	277 (38%)	283 (38%)	270 (37%)
Estimated pack-years	45 (23)	44 (23)	47 (28)
Prebronchodilator FEV_1 (L)	0·91 (0·30)	0·90 (0·30)	0·89 (0·30)
Postbronchodilator FEV_1 (L)	1·04 (0·30)	1·04 (0·30)	1·04 (0·30)
Postbronchodilator FEV_1 (% predicted)	37·0% (8·1)	37·3% (8·1)	37·4% (8·1)
Pre/postbronchodilator FEV_1 reversibility (%)	17·2% (19·6)	18·8% (19·1)	18·9% (19·3)
FEV_1/FVC (%), post-bronchodilator	39·3% (9·2)	39·3% (9·6)	39·3% (9·6)
SGRQ total score at baseline†	53 (18)	52 (18)	52 (17)
Use of rescue salbutamol at baseline (puffs per day)‡	5·7 (4·6)	5·7 (5·0)	5·5 (4·7)

SPARK study. Lancet Respir Med 2013;1:199-209

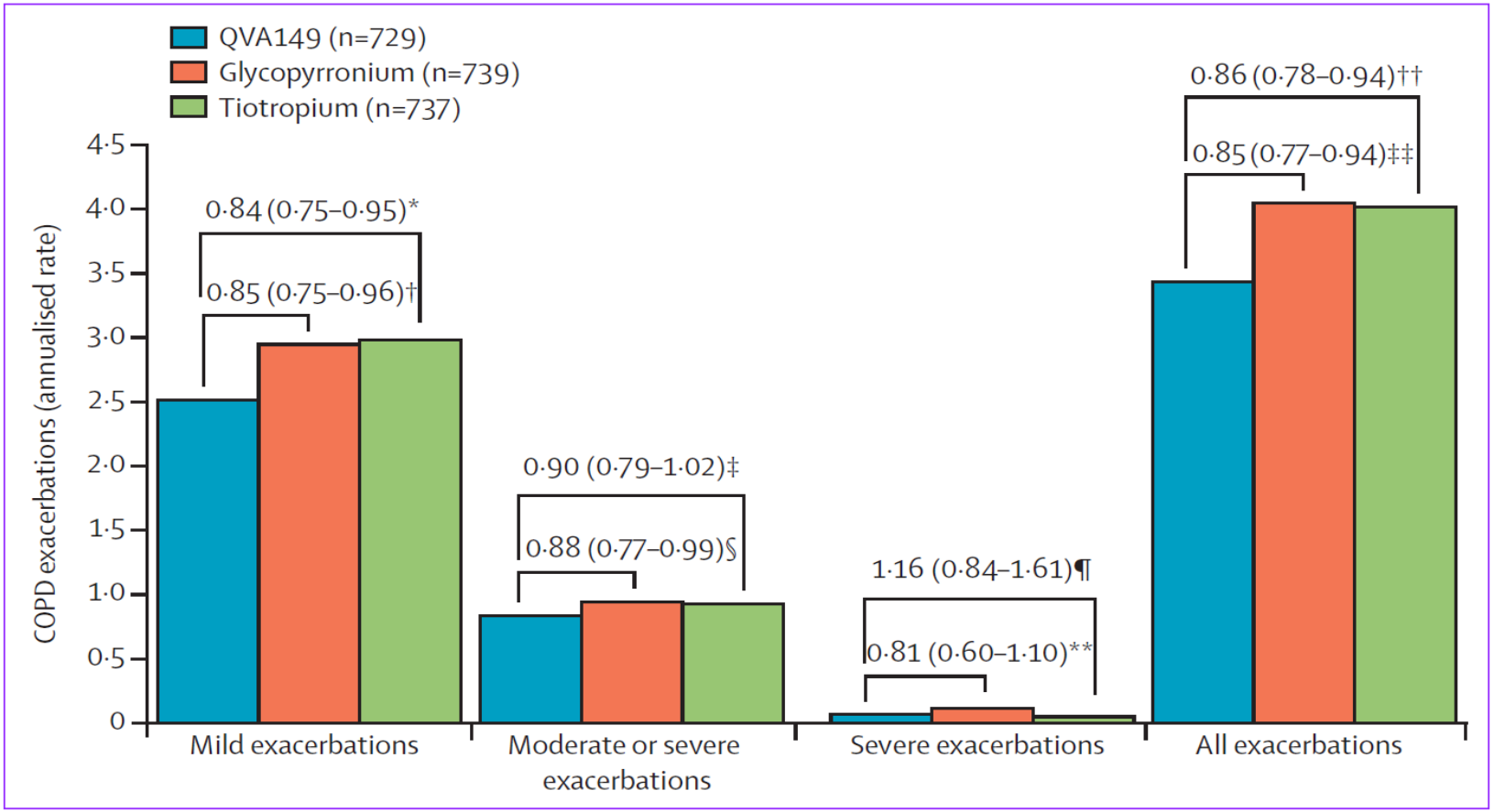
Exacerbation rate between groups

	Total number of exacerbations	Mean number of exacerbations per patient	Annualised rate (95% CI)*
Mild exacerbations (6969 events)			
QVA149 (n=729)	2105	2·89 (3·50)	2·51 (2·25–2·80)
Glycopyrronium (n=739)	2422	3·28 (3·89)	2·96 (2·66–3·29)
Tiotropium (n=737)	2442	3·31 (3·97)	2·98 (2·68–3·32)
Moderate or severe exacerbations (2610 events)			
QVA149 (n=729)	812	1·11 (1·35)	0·84 (0·75–0·94)
Glycopyrronium (n=739)	900	1·22 (1·48)	0·95 (0·85–1·06)
Tiotropium (n=737)	898	1·22 (1·66)	0·93 (0·83–1·04)
Severe exacerbations (364 events)			
QVA149 (n=729)	121	0·17 (0·47)	0·09 (0·07–0·13)
Glycopyrronium (n=739)	138	0·19 (0·49)	0·12 (0·09–0·16)
Tiotropium (n=737)	105	0·14 (0·47)	0·08 (0·06–0·11)
All exacerbations† (9488 events)			
QVA149 (n=729)	2893	3·97 (3·88)	3·44 (3·15–3·75)
Glycopyrronium (n=739)	3294	4·46 (4·39)	4·04 (3·71–4·40)
Tiotropium (n=737)	3301	4·48 (4·51)	4·02 (3·69–4·38)

	QVA149 *vs* glycopyrronium	QVA149 *vs* tiotropium	Glycopyrronium *vs* tiotropium
Mild exacerbations	0·85 (0·75–0·96; 0·0072)	0·84 (0·75–0·95; 0·0052)	0·99 (0·88–1·12; 0·90)
Moderate or severe exacerbations	0·88 (0·77–0·99; 0·038)	0·90 (0·79–1·02; 0·096)	1·03 (0·91–1·16; 0·68)
Severe exacerbations	0·81 (0·60–1·10; 0·18)	1·16 (0·84–1·61; 0·36)	1·43 (1·05–1·97; 0·025)
All exacerbations	0·85 (0·77–0·94; 0·0012)	0·86 (0·78–0·94; 0·0017)	1·01 (0·91–1·11; 0·92)

SPARK study. Lancet Respir Med 2013;1:199-209

Annualised rate of COPD exacerbations, by treatment group



Values are rate reduction (95% CI; p value). *p=0·0052. †p=0·0072. ‡p=0·096. §p=0·038. ¶p=0·36. **p=0·18. ††p=0·0017. ‡‡p=0·0012.

SPARK study. Lancet Respir Med 2013;1:199-209

LAMA vs. ICS+LABA for GOLD C,D

Tiotropium vs. ICS+LABA

	Duration	N	ICS/LABA	Inclusion criteria	Mean FEV1	Primary outcome
Fang 2008	18 mo	80	Seretide	25%≤FEV1≤70%		PFT, worsening, AE
INSPIRE 2008	104 wk	1323	Seretide	FEV1<50% and history of COPD exacerbations	39%	To compare the rate of health care utilization exacerbation
SCO40034	12 wk	125	Seretide	FEV1<70%		

Cochrane review 2013

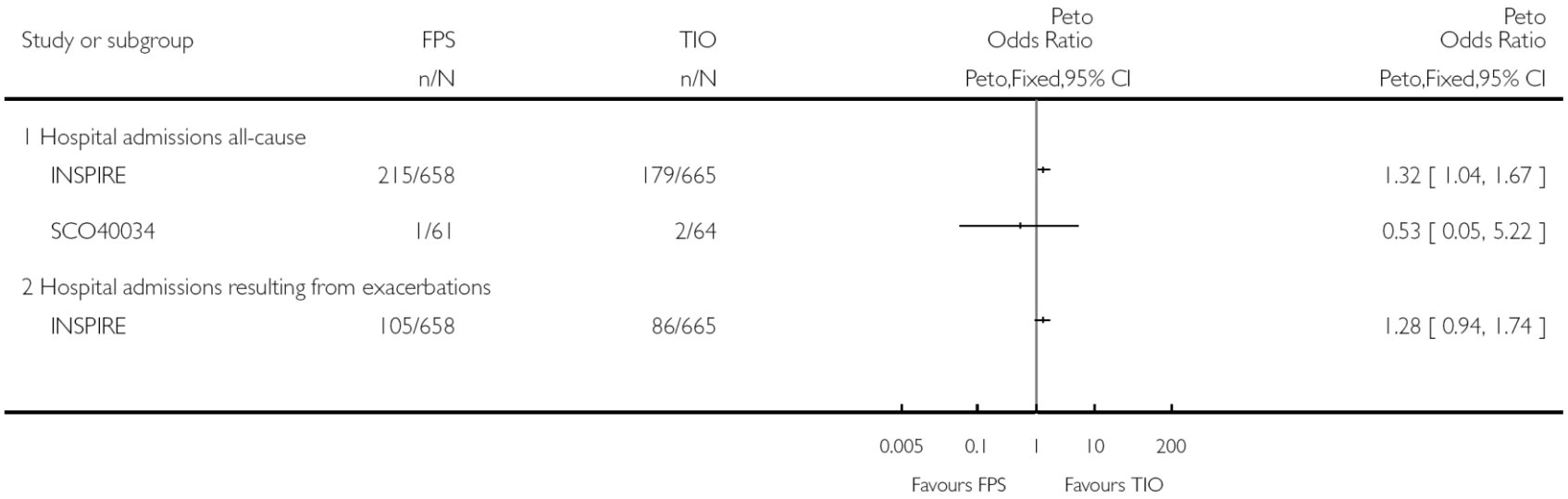
Patients characteristics

Parameter	SFC (*n* = 658)	Tiotropium (*n* = 665)
Age, yr, mean	64	65
Males, %	81	84
Post-bronchodilator FEV_1, L, mean	1.11	1.13
Post-bronchodilator FEV_1, % predicted, mean	39.1	39.4
Reversibility, % predicted, mean	2.34	2.63
⩾1 Exacerbation in the 12 mo before study start, %	85	88
Prebronchodilator FEV_1, L, mean		
All patients	1.05	1.06
GOLD stage III (⩾30 to <50% predicted)	1.09 (n = 540)	1.11 (n = 537)
GOLD stage IV (<30% predicted)	0.73 (n = 100)	0.71 (n = 101)
Current smokers, %	38	38
Smoking history, pack-years, mean	41.3	39.5
SGRQ score at baseline,* mean	48.6	49.1
Patients discontinuing ICS at entry, n (%)	319 (48)	340 (51)

INSPIRE study. Am J Respir Crit Care Med 2008:177;19-26

Tiotropium vs. ICS+LABA

Hospital Admission

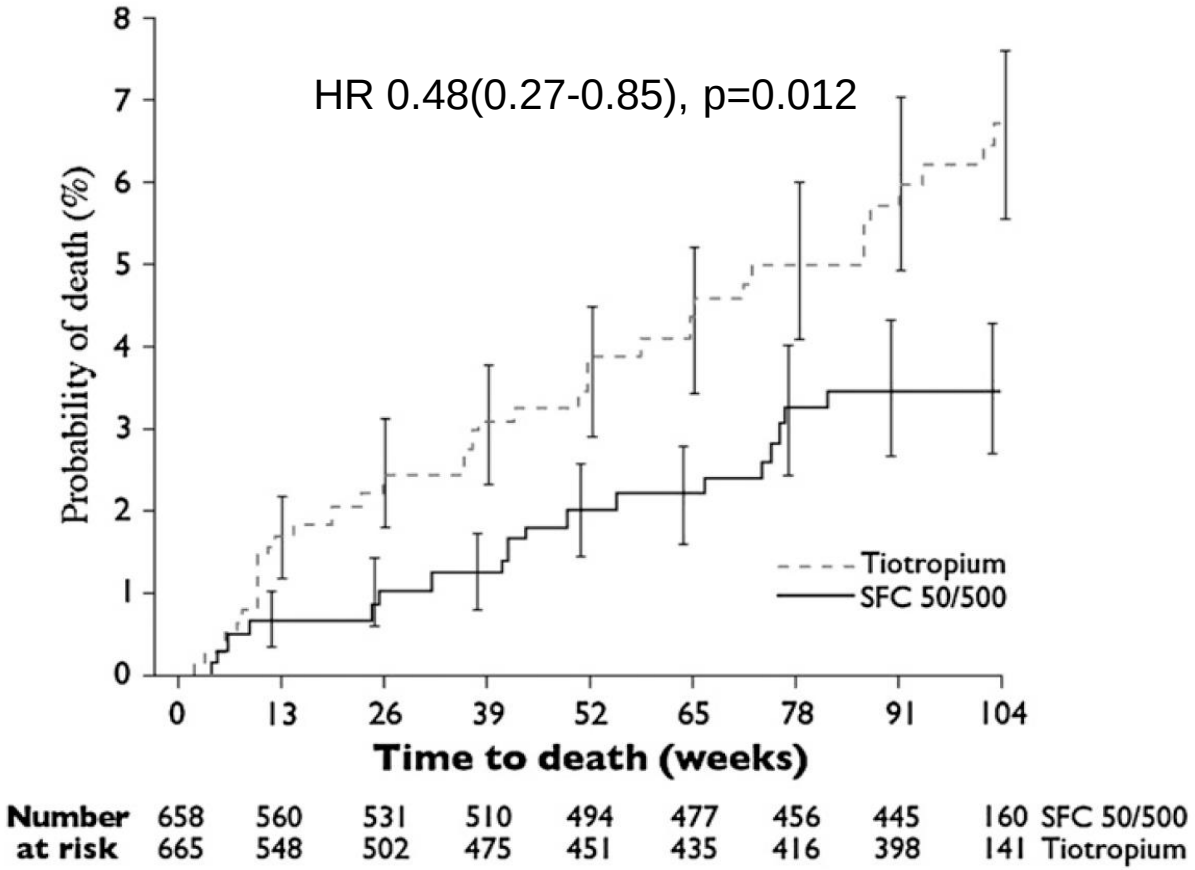


Variable	SFC 50/500 ($n = 658$)	Tiotropium ($n = 665$)	Rate Ratio*	95% CI	*P* Value
		Exacerbations (*mean no./yr*)			
HCU	1.28	1.32	0.97	0.84 to 1.12	0.656
Requiring oral corticosteroids	0.69	0.85	0.81	0.67 to 0.99	0.039
Requiring antibiotics	0.97	0.82	1.19	1.02 to 1.38	0.028

Cochrane Review 2013

INSPIRE study. Am J Respir Crit Care Med 2008:177;19-26

ICS/LABA vs. tiotropium on mortality



INSPIRE study. Am J Respir Crit Care Med 2008:177;19-26

LAMA vs. ICS+LABA+LABA for GOLD C,D

ICS+LABA+Tiotropium vs. Tiotropium

	Duration	N	ICS+LABA	Inclusion criteria	Mean FEV1	Primary outcome
Aaron 2007	52 wk	449	Seretide	FEV1≤65% and ≥ 1 exacerbation within previous yr	39%	Proportion of patients with one or more AECOPD
Cazzola 2007	12 wk	90	Seretide	FEV1≤50%	38%	FEV1, dyspnea
Welte 2009	12 wk	660	symbicort	FEV1≤50%	38%	FEV1

Cochrane review 2013

Tiotropium + LABA+ ICS vs. Tiotropium for COPD

Outcomes	Illustrative comparative risks (95%CI)		Relative effect (95%CI)	No of participants
	Assumed risk	Corresponding risk		
	Tio+placebo	Tio+ICS/LABA		
Mortality (all cause)	8/1000	15/1000 (5 to48)	OR 1.88 (0.57-6.23)	1021
Hospital admission (all cause)	103/1000	88/1000 (57 to 132)	OR 0.84 (0.53-1.33)	961
Hospital admission (exacerbation)	78/1000	53/1000 (32 to 87)	OR 0.66 (0.39-1.13)	961
pneumonia	6/1000	8/1000 (2 to 35)	OR 1.35 (0.31-5.99)	961

Cochrane review 2013

ICS+LAMA vs. ICS+LABA for GOLD C,D

Once-daily indacaterol versus tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE): a randomised, blinded, parallel-group study

- 52 wks multicentre, randomised, blinded, double-dummy, parallel group study
- Severe COPD patients with age ≥ 40 years and ≥ 1 exacerbation within the previous year
- N=3,439, mean FEV1 : 40.5% predicted, Allowed ICS (72% used)
- Indacaterol (150 µg) vs. Tiotropium (18 µg) once daily
- Indacaterol was noninferior to tiotropium
  - for trough FEV1 at week 12 (primary endpoint)
  - for rate of exacerbations at week 52 (secondary endpoint).

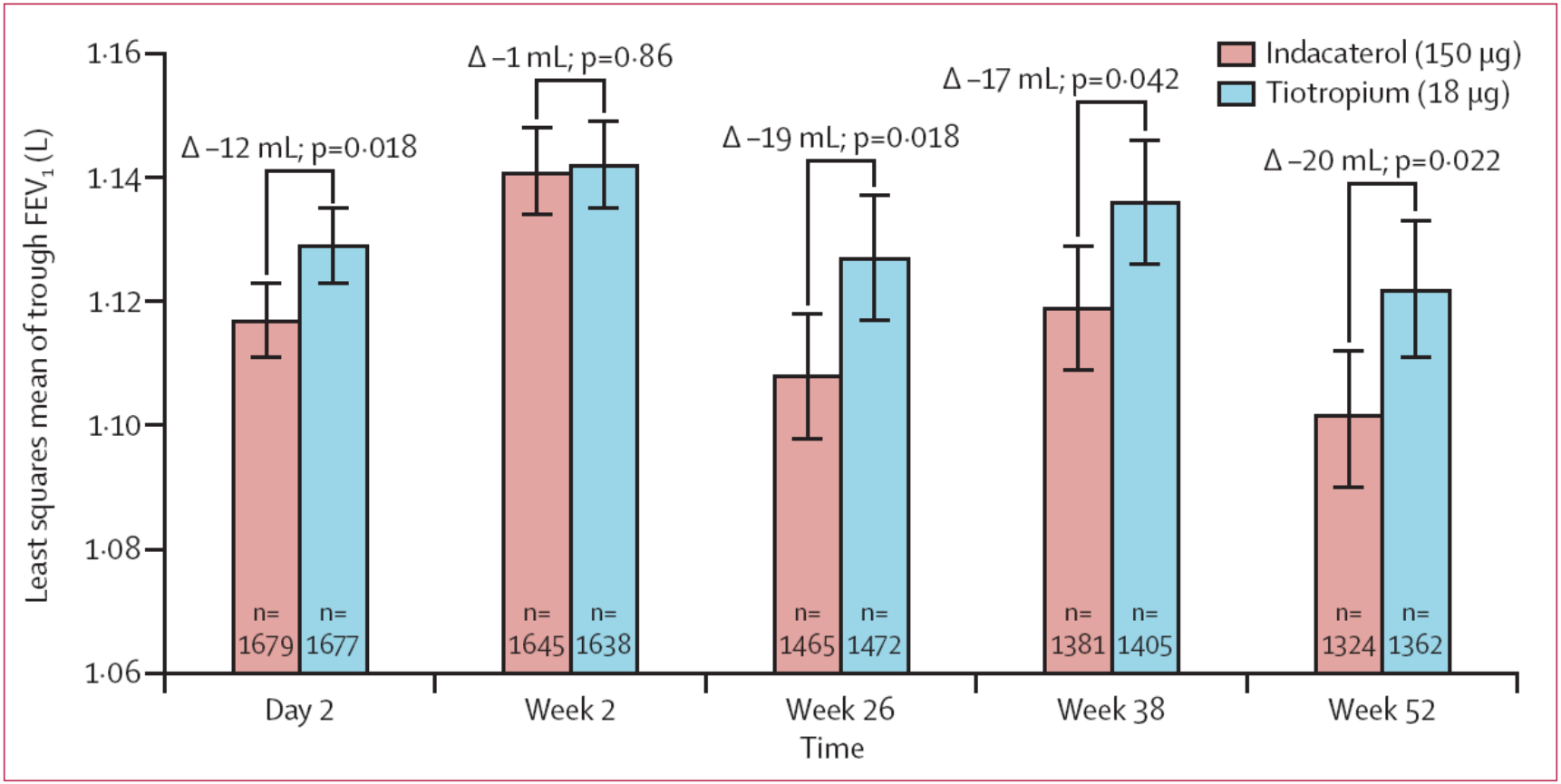
INVIGORATE study. Lancet Respir Med 2013;1: 524-33

Baseline characteristics

	Indacaterol (n=1721)	Tiotropium (n=1718)	All patients (n=3439)
Number COPD exacerbations in previous year			
0	6 (<0·5%)	7 (<0·5%)	13 (<0·5%)
1	1365 (79%)	1342 (78%)	2707 (79%)
2	244 (14%)	251 (15%)	495 (14%)
3	59 (3%)	69 (4%)	128 (4%)
≥4	47 (3%)	49 (3%)	96 (3%)
Median (range)	1·00 (1·00–10)	1·00 (1·00–10)	1·00 (1·00–10)
Baseline spirometry (post-bronchodilator)			
FEV_1 (mean litres [SD])	1·133 (0·278)	1·138 (0·280)	1·136 (0·279)
FEV_1 (mean % predicted [SD])	40·2 (6·01)	40·7 (6·06)	40·5 (6·04)
<30%	19 (1%)	20 (1%)	39 (1%)
30 to <50%	1680 (98%)	1679 (98%)	3359 (98%)
50 to <80%	17 (1%)	14 (1%)	31 (1%)
≥80%	0	0	0
Missing	5 (<0·5%)	5 (<0·5%)	10 (<0·5%)
FEV_1 to FVC ratio (mean [SD])	46·0 (9·67)	46·5 (9·77)	46·3 (9·72)
Inhaled corticosteroids use			
Yes	1235 (72%)	1234 (72%)	2469 (72%)
No	486 (28%)	484 (28%)	970 (28%)
Baseline SGRQ total score	1664	1669	3333
Mean (SD)	47·9 (17·4)	48·7 (17·8)	48·3 (17·6)

INVIGORATE study. Lancet Respir Med 2013;1: 524-33

Trough FEV1



INVIGORATE study. Lancet Respir Med 2013;1: 524-33

Indacaterol vs. Tiotropium -exacerbation-

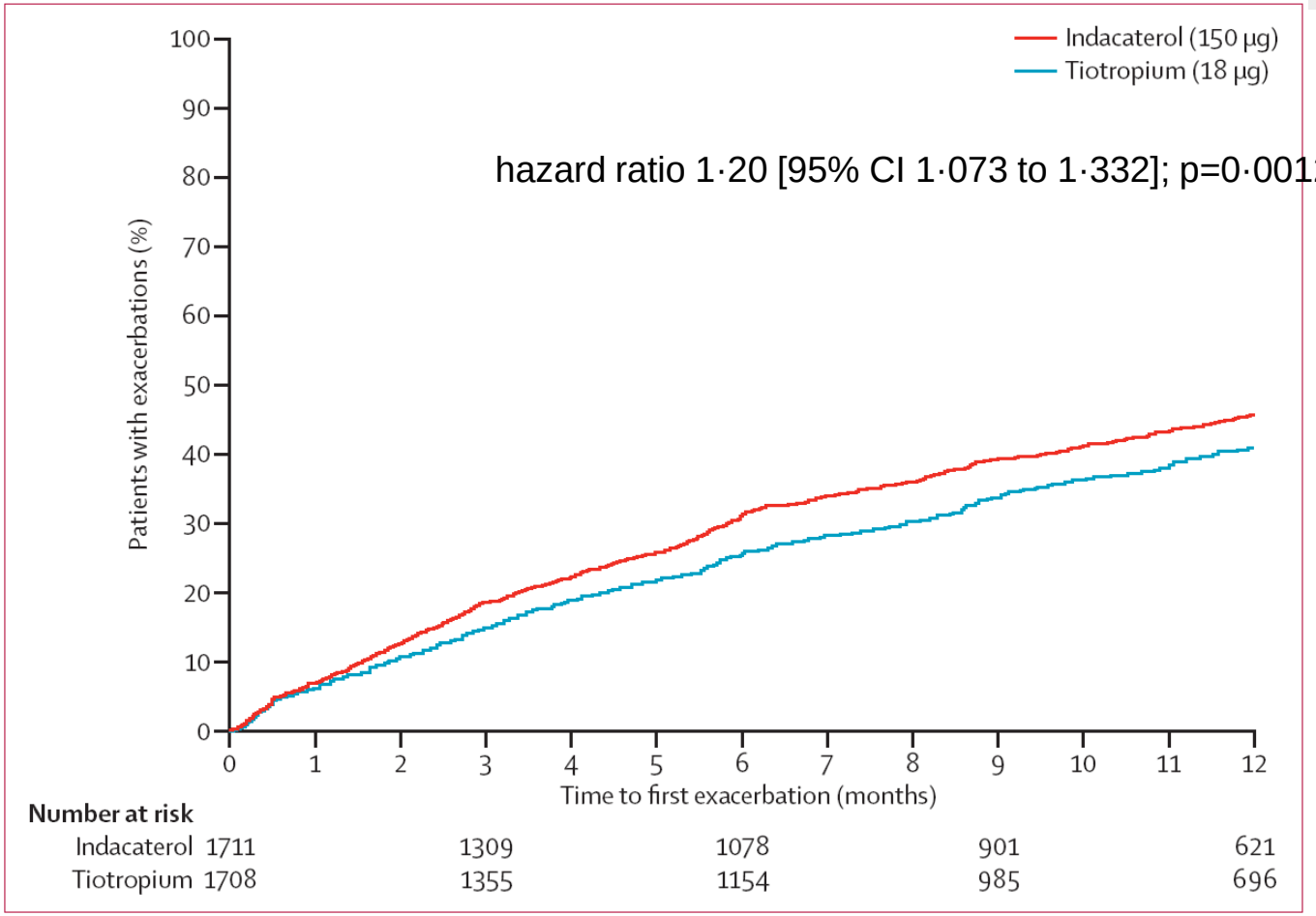
	Indacaterol (n=1529)	Tiotropium (n=1543)	Treatment difference
Treatment comparison non-inferiority to tiotropium			
Number included in the analysis	1520	1533	..
Rate (negative binomial model)	0·79	0·61	..
Rate ratio (indacaterol/tiotropium)	..	..	1·29
Upper limit of 97·5% CI	..	..	1·44
p value	..	..	0·99
Number of exacerbations per patient (without imputation; n [%])			
None	910 (60%)	996 (65%)	..
1	381 (25%)	347 (23%)	..
2	139 (9%)	142 (9%)	..
3	59 (4%)	43 (3%)	..
≥4	40 (3%)	15 (1%)	..
Total number of exacerbations	1026	830	..
Total number of treatment years	1372·50	1397·64	..

Non-inferiority of indacaterol (150 µg) to tiotropium (18 µg) is shown if the upper limit of the 97·5% CI is lower than 1·12 (ie, the upper limit is less than a 12% increase in exacerbation rate compared with tiotropium)

Table 2: **Number and rate of exacerbations per patient during 52 weeks (non-inferiority comparison)**

INVIGORATE study. Lancet Respir Med 2013;1: 524-33

Indacaterol vs. Tiotropium -time to first exacerbation-



INVIGORATE study. Lancet Respir Med 2013;1: 524-33

Health status and dyspnoea

	Indacaterol (150 µg)		Tiotropium (18 µg)		Treatment difference		
	Number of patients	Mean*	Number of Patients	Mean*	LS mean (SE); 95% CI	Odds ratio (95% CI)	p value
Health status							
SGRQ total score: % patients with improvement ≥4 units							
Week 12	732/1496 (49%)	..	725/1503 (48%)	..	..	1·06 (0·92 to 1·24)	0·41
Week 26	673/1408 (48%)	..	707/1421 (50%)	..	..	0·95 (0·81 to 1·11)	0·51
Week 38	638/1328 (48%)	..	672/1357 (50%)	..	..	0·97 (0·83 to 1·13)	0·69
Week 52	626/1273 (49%)	..	646/1314 (49%)	..	..	1·03 (0·88 to 1·21)	0·72
Dyspnoea							
TDI total score: % patients with improvement ≥1							
Week 12	896/1513 (59%)	..	861/1511 (57%)	..	..	1·10 (0·95 to 1·27)	0·21
Week 26	817/1427 (57%)	..	811/1436 (57%)	..	..	1·04 (0·89 to 1·20)	0·64
Week 38	755/1347 (56%)	..	750/1368 (55%)	..	..	1·06 (0·91 to 1·23)	0·48
Week 52	745/1288 (58%)	..	728/1322 (55%)	..	..	1·12 (0·96 to 1·31)	0·15

INVIGORATE study. Lancet Respir Med 2013;1: 524-33

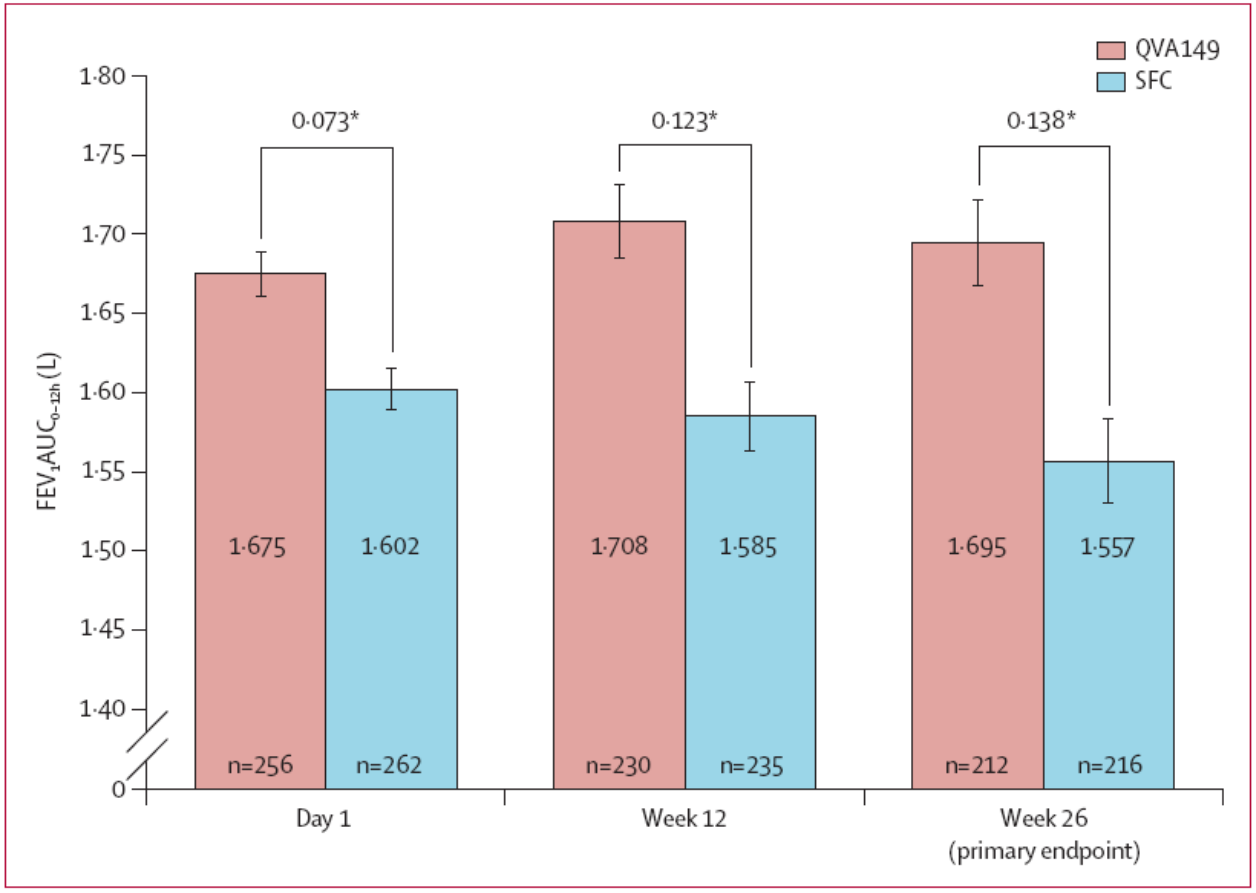
LAMA+LABA vs. ICS+LABA

Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol–fluticasone in patients with chronic obstructive pulmonary disease (ILLUMINATE): a randomised, double-blind, parallel group study

- 26 weeks, multicentre double-blind, double-dummy, parallel-group study
- GOLD II-III without exacerbations in the previous year
- N= 523, meanFEV1 = 60.2% predicted
  - GOLD II 80.2%/80.3%, GOLD III 19.8%/19.7%
- QVA149 (indacaterol+glycopyrronium) 110/50 µg qd vs. SFC 50/500 µg bid
- Primary endpoint : superiority of QVA149 for the standardised area under the curve from 0 to 12 h post dose for FEV1

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

Once-daily QVA149 provides significant, sustained, and clinically meaningful improvements in lung function



* p<0.0001

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

Once-daily QVA149 provides significant symptomatic benefit

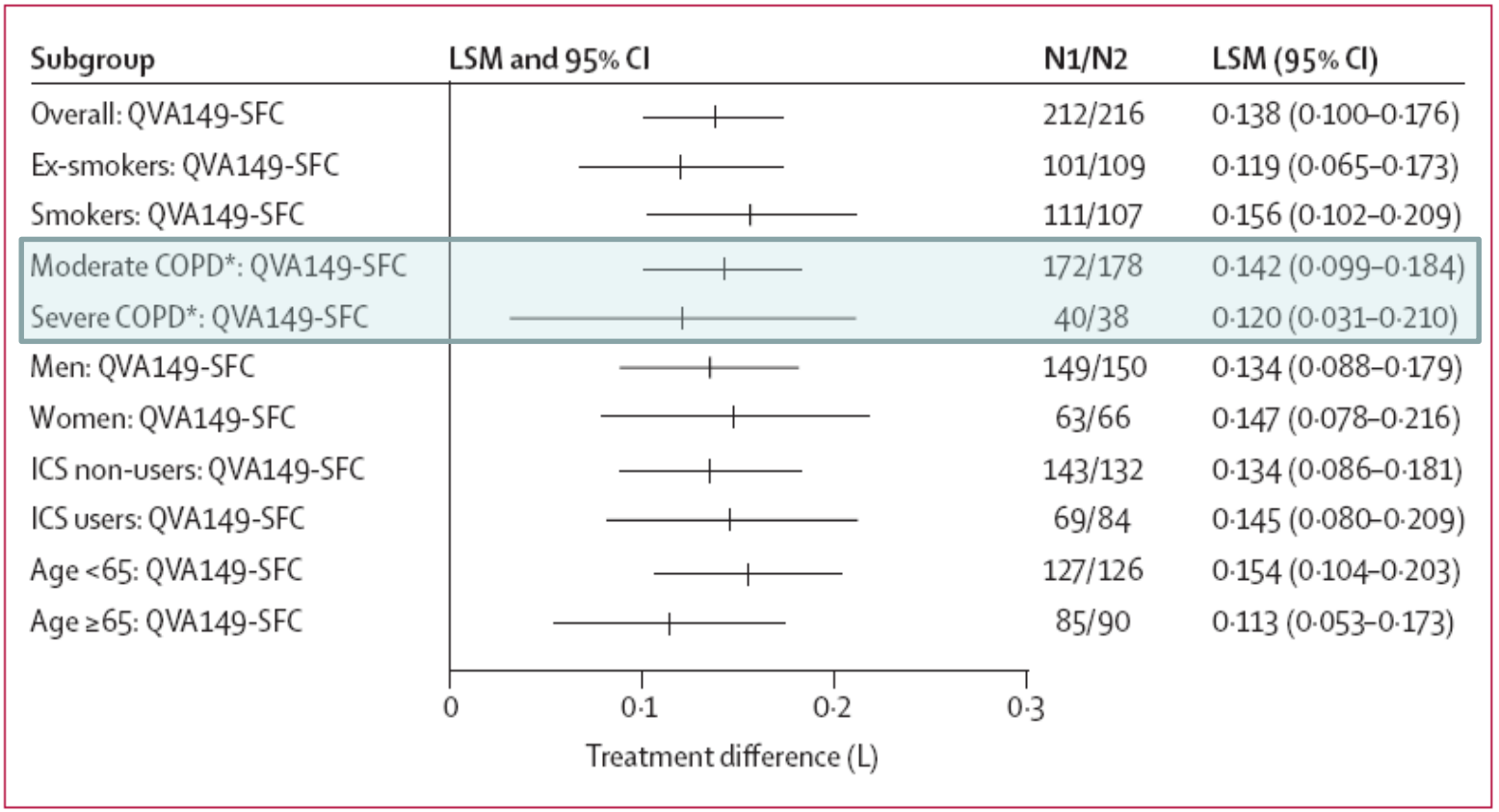
	Day 1		Week 12		Week 26	
	Treatment difference QVA149 versus SFC (LSM [95% CI])	p value for treatment comparison	Treatment difference QVA149 versus SFC (LSM [95% CI])	p value for treatment comparison	Treatment difference QVA149 versus SFC (LSM [95% CI])	p value for treatment comparison
FEV_1 AUC_{0-12h} (L)*	0·073 (0·051 to 0·096)	<0·0001	0·123 (0·090 to 0·155)	<0·0001	0·138 (0·100 to 0·176)	<0·0001
Peak FEV_1 (L)*	0·066 (0·043 to 0·089)	<0·0001	0·145 (0·112 to 0·179)	<0·0001	0·155 (0·115 to 0·194)	<0·0001
Pre-dose trough FEV_1 (L)*	..	..	0·092 (0·059 to 0·125)	<0·0001	0·103 (0·065 to 0·141)	<0·0001
FEV_1 (L) 5 min post-dose	0·081 (0·064 to 0·098)	<0·0001	0·129 (0·095 to 0·163)	<0·0001	0·150 (0·110 to 0·191)	<0·0001
FEV_1 (L) 30 min post-dose	0·075 (0·054 to 0·097)	<0·0001	0·157 (0·122 to 0·193)	<0·0001	0·161 (0·121 to 0·201)	<0·0001
FVC AUC_{0-12h} (L)	0·086 (0·036 to 0·136)	0·00076	0·196 (0·132 to 0·261)	<0·0001	0·201 (0·131 to 0·271)	<0·0001
Peak FVC (L)	0·062 (0·010 to 0·115)	0·021	0·210 (0·141 to 0·280)	<0·0001	0·217 (0·142 to 0·292)	<0·0001
Pre-dose trough FVC (L)	..	..	0·199 (0·137 to 0·260)	<0·0001	0·196 (0·131 to 0·261)	<0·0001
TDI focal score*	..	..	0·58 (0·07 to 1·08)	0·025	0·76 (0·26 to 1·26)	0·0031
SGRQ-C total score	..	..	0·71 (–0·99 to 2·41)	0·41	–1·24 (–3·33 to 0·85)	0·25
Change from baseline in rescue medication use, puffs/day	..	..	–0·28 (–0·59 to 0·04)	0·089	–0·39 (–0·71 to –0·06)	0·019
Change from baseline in daytime rescue medication use, puffs/day	..	..	–0·26 (–0·45 to –0·07)	0·0084	–0·32 (–0·52 to –0·13)	0·0013

*Minimum clinically important difference is 100 mL (FEV_1)[11] and 1-point (TDI score).[12] SFC=salmeterol–fluticasone. LSM=least squares mean. FEV_1=forced expiratory volume in 1 second. AUC_{0-12h}=area under the curve from 0 to 12 h. FVC=forced vital capacity. TDI=transition dyspnoea index. SGRQ-C=St George's Respiratory Questionnaire for COPD patients (a reduction indicates improvement).

Table 2: **Primary and secondary efficacy outcomes in the ILLUMINATE study**

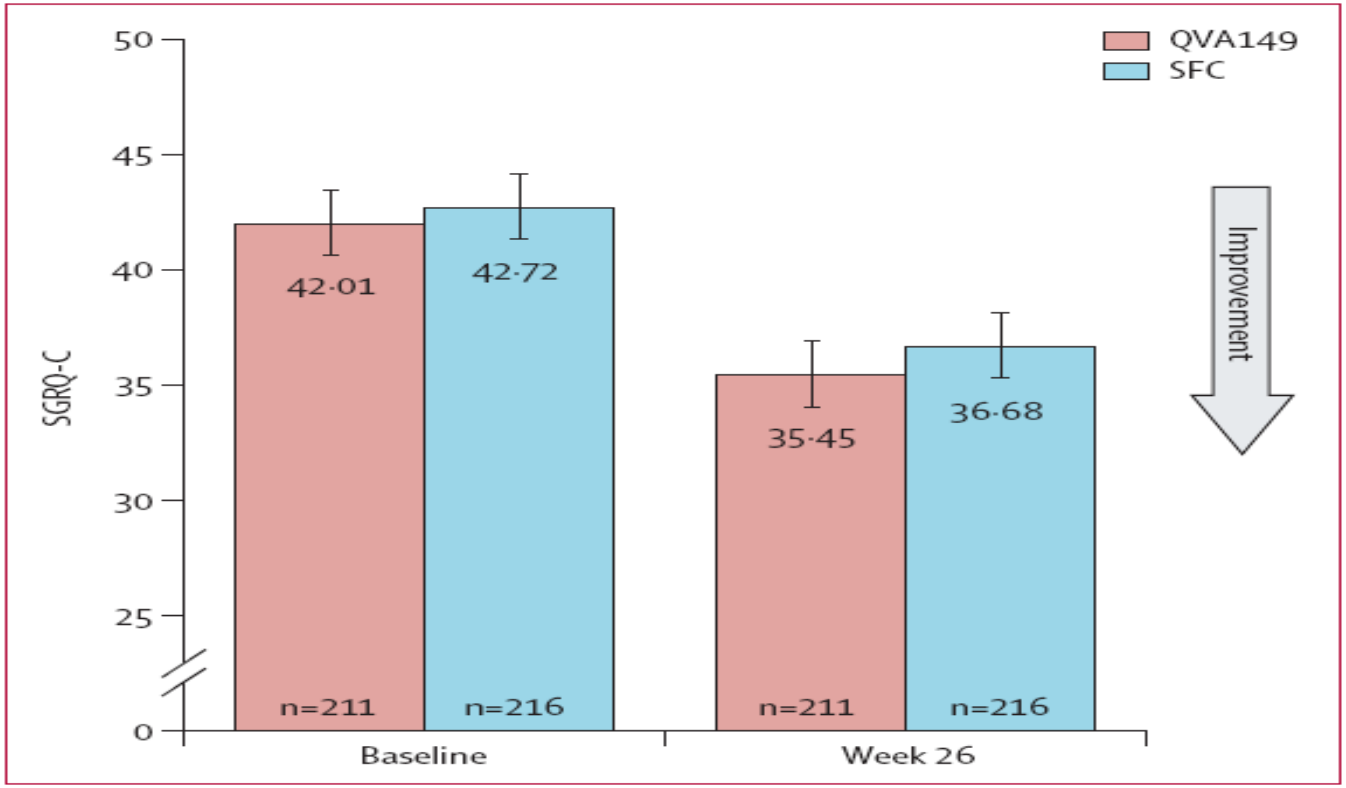
ILLUMINATE study. Lancet Respir Med 2013;1:51-60

Treatment differences in FEV1 AUC_{0-12h} by subgroup at week 26



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

Mean SGRQ-C total score



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

Summary

- Tiotropium is more effective than salmeterol in preventing exacerbations.
- Indacaterol and tiotropium are equally effective at providing clinically-relevant improvements in lung function and health outcomes. However, tiotropium gives better protection from exacerbations
- Compared with tiotropium monotherapy, indacaterol plus tiotropium provides greater bronchodilation and lung deflation
- There is no difference in exacerbation rate between salmeterol/fluticasone and tiotropium.

Summary

- Dual bronchodilation with once-daily QVA149 is superior in preventing moderate to severe COPD exacerbations compared with the glycopyrronium, with concomitant improvements in lung function and health status.
- QVA149 provides significant, sustained, and clinically meaningful improvements in lung function versus twice-daily salmeterol/fluticasone.
- The addition of ICS+LABA combination treatment to tiotropium has shown improvements in average health-related quality of life and lung function.