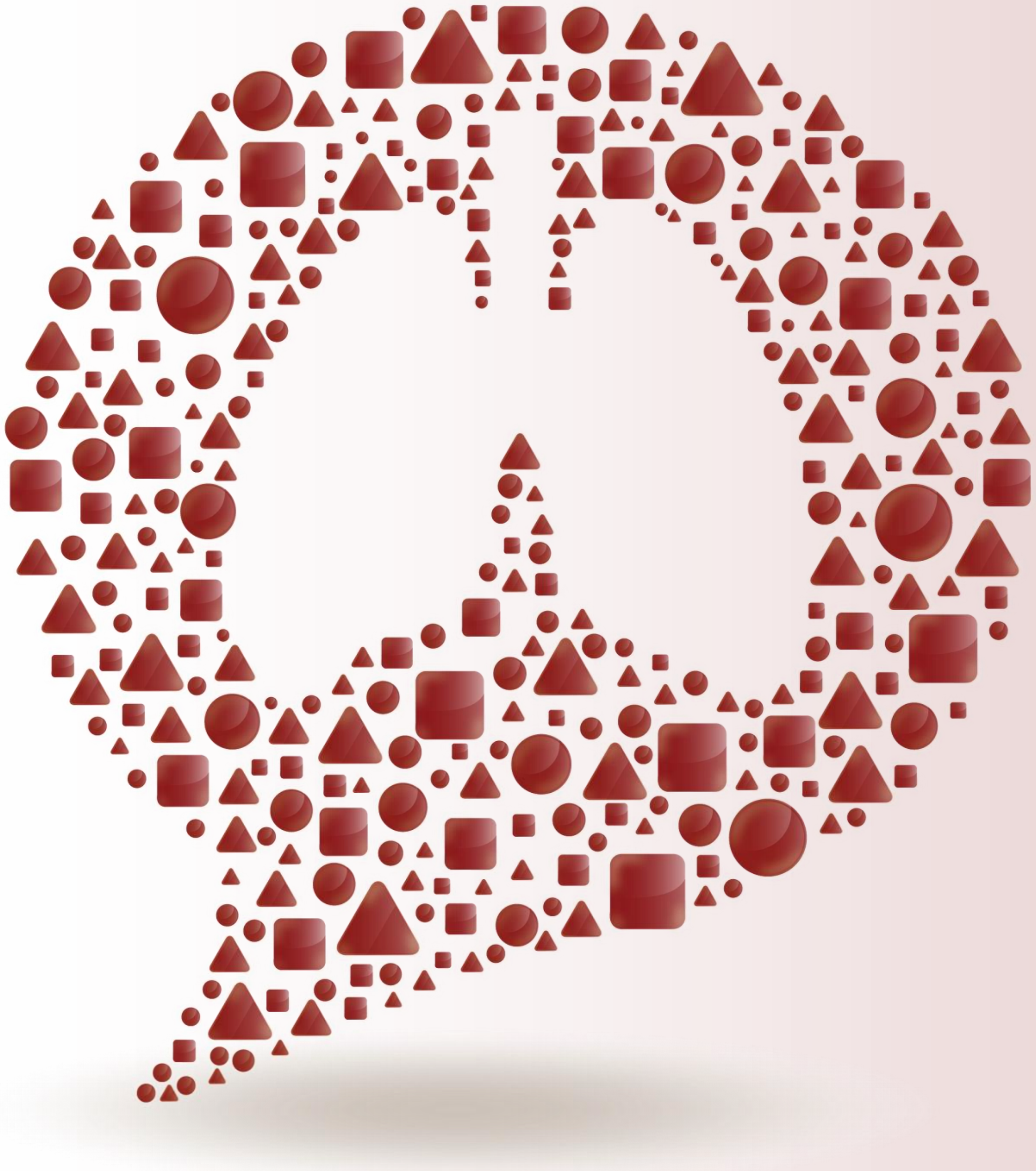


Advancing COPD treatment strategies with evidence-based approaches

17:15–19:15 Monday 11 September 2017

ERS 2017, Milan, Italy

Addressing the needs of COPD patients with a lower exacerbation risk

Claus F Vogelmeier

August 2017
GLRESP/COPD/0246k

Conflict of interest statement

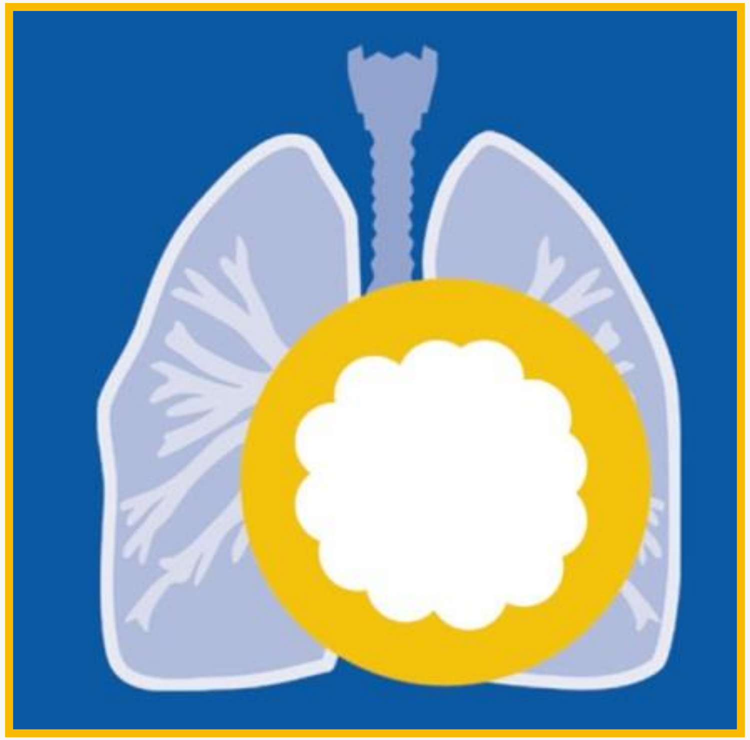
Consultancy: Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Grifols, Janssen, Mundipharma, Novartis, OmniaMed, Takeda, Menarini, Teva and MedUpdate

Grants and unrestricted funding for investigator-initiated studies: AstraZeneca, GlaxoSmithKline and Grifols

Lectures: Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Grifols, Janssen, Mundipharma, Novartis, OmniaMed, Takeda, Menarini, Teva and MedUpdate

Addressing the needs of patients with a lower exacerbation risk

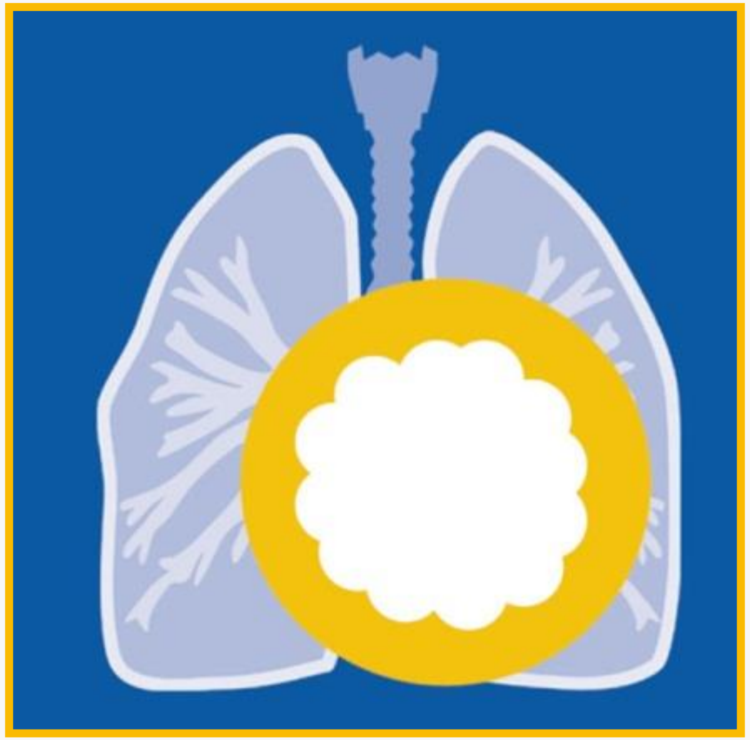
- GOLD A/B patients
  - Burden of disease
  - Treatment recommendations
  - ICS withdrawal



GOLD = Global initiative for chronic Obstructive Lung Disease; ICS = inhaled corticosteroid

Addressing the needs of patients with a lower exacerbation risk

- GOLD A/B patients
  - Burden of disease



The GOLD refined ABCD assessment tool

Spirometrically confirmed diagnosis → **Assessment of airflow limitation** → **Assessment of symptoms/risk of exacerbations**

Post-bronchodilator $FEV_1/FVC < 0.7$

	FEV_1 (% predicted)
GOLD 1	≥80
GOLD 2	50–79
GOLD 3	30–49
GOLD 4	<30

Exacerbation history		
≥2 or ≥1 leading to hospital admission	**C**	**D**
0 or 1 (not leading to hospital admission)	**A**	**B**
	mMRC 0–1 CAT < 10	mMRC ≥ 2 CAT ≥ 10

Symptoms

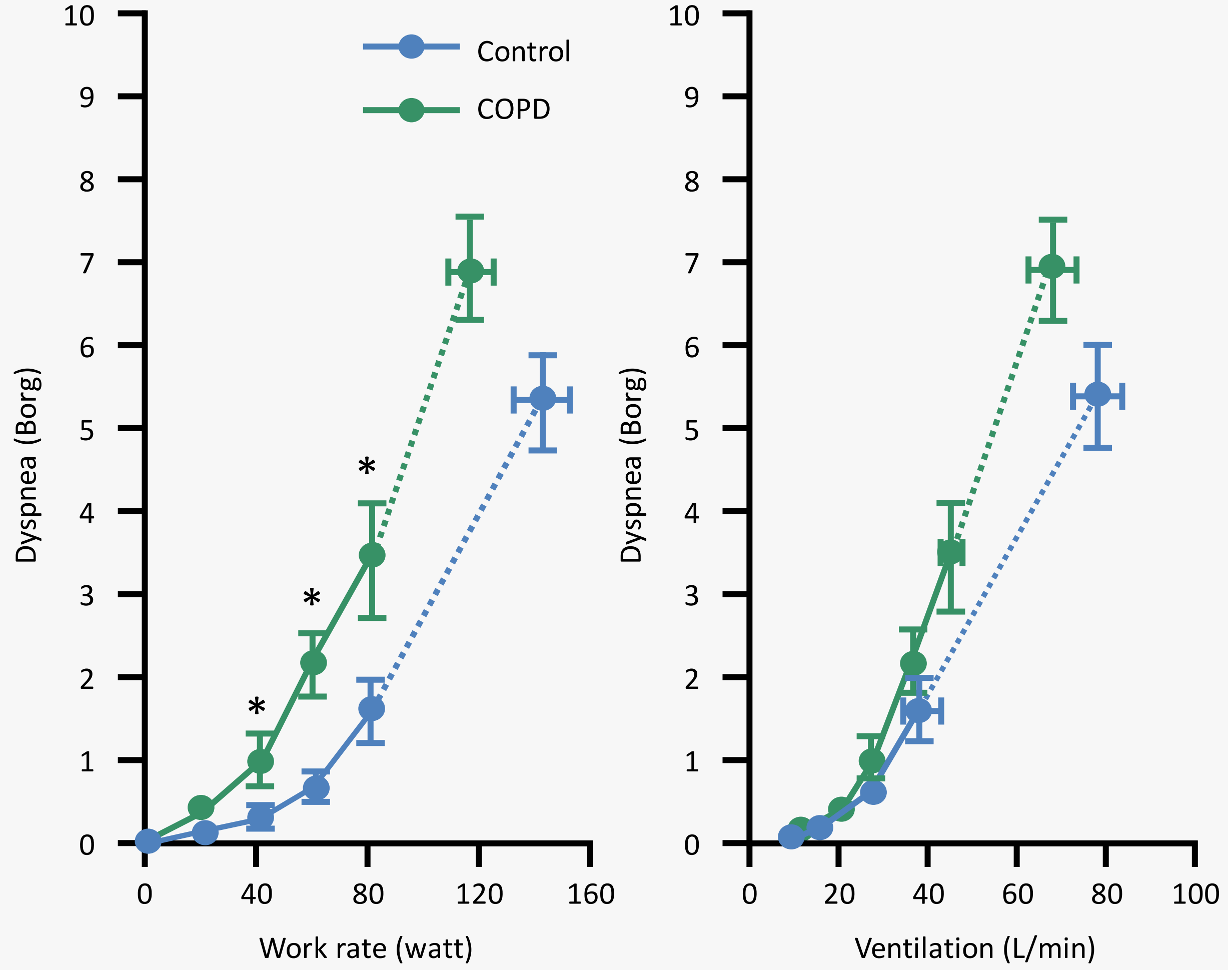
CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; mMRC = modified Medical Research Council;
GOLD. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2017. Available at: http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/

Mechanisms of dyspnea during exercise in symptomatic patients with GOLD Stage I COPD

21 COPD-Pts. GOLD Stage I‡
Post BD FEV_1 91%, FEV_1/FVC 60%
21 controls

Incremental cycle exercise

- **Dyspnea vs. work rate**
- **Dyspnea vs. ventilation**



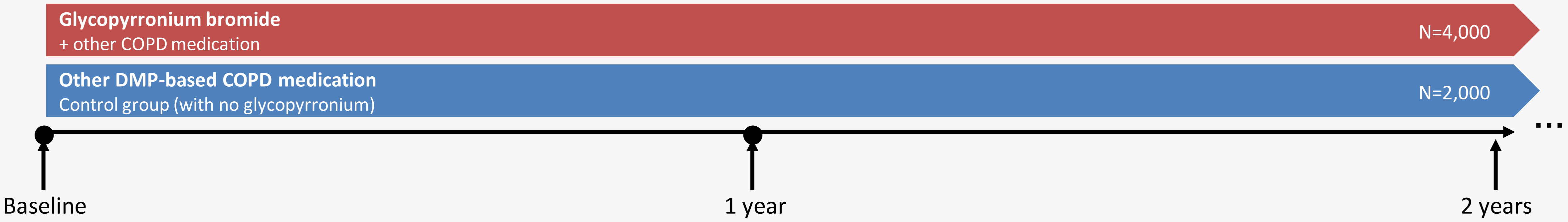
*P <0.05 COPD vs control;
‡ Defined as PB FEV_1 ≥80% predicted and FEV_1/FVC <0.7 as per GOLD guidelines (2007)

Ofir D, et al. AJRCCM 2008;177:622–9

Real life German COPD population: DACCORD registry

Study design/methods

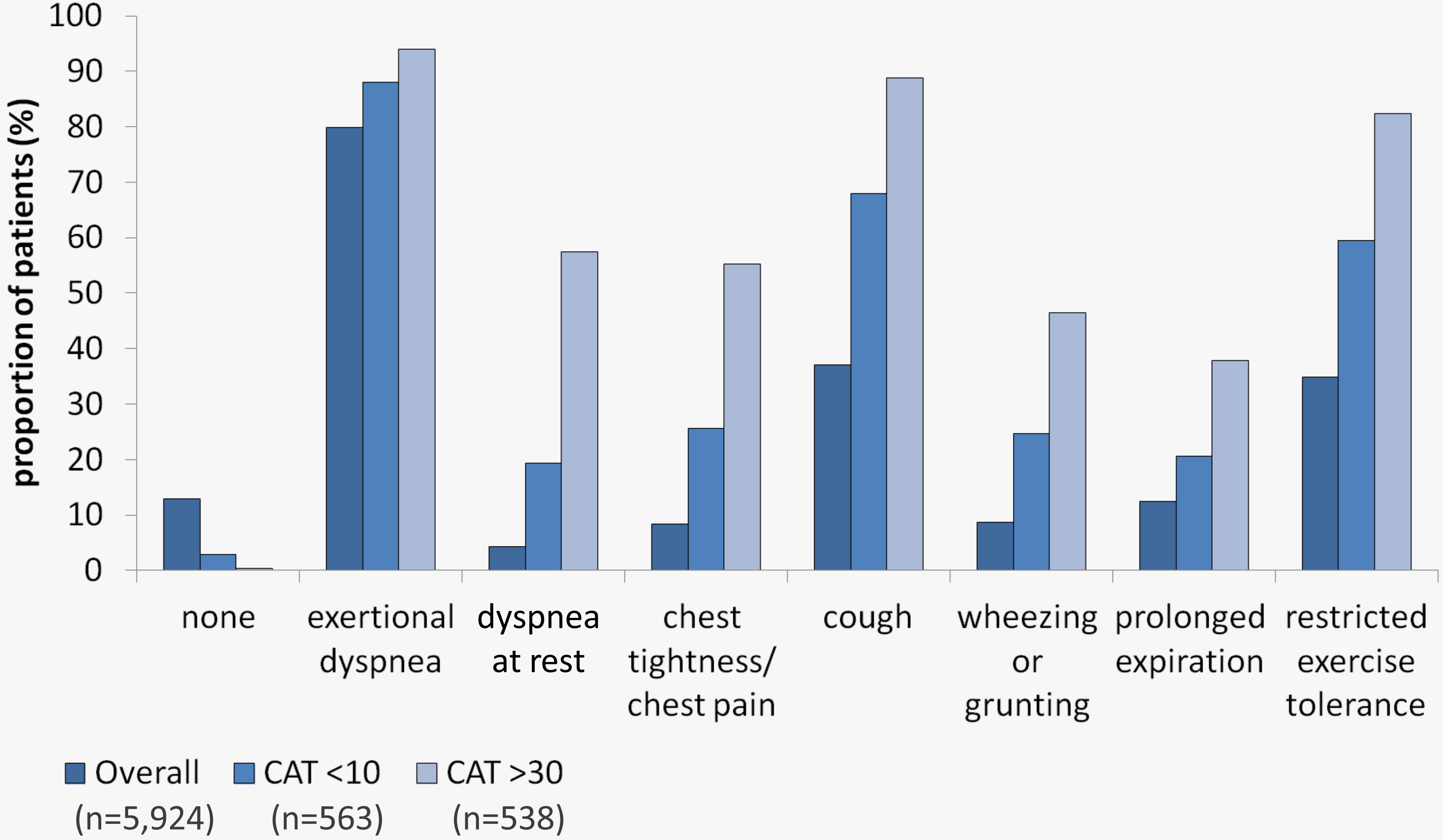
- National, prospective non-interventional cohort study in primary and secondary care
- Inclusion criteria:
  - Written informed consent of the patient for participation in the study
  - Age ≥40 years
  - Diagnosis of COPD confirmed by the physician fulfilling the German COPD Disease Management Program criteria
  - Beginning or modification of COPD maintenance therapy at study start (Visit 0)
- 6,000 patients, enrolment 2:1 (with glycopyrronium: without glycopyrronium)
- Collected data included spirometry, history of exacerbations, CAT, symptoms and comorbidities



DMP = Disease Management Program

Worth H, et al. Respir Med 2016;111:64–71

Real life German COPD population: DACCORD registry – symptoms



Worth H, et al. Respir Med 2016;111:64–71

Addressing the needs of patients with a lower exacerbation risk

- GOLD A/B patients
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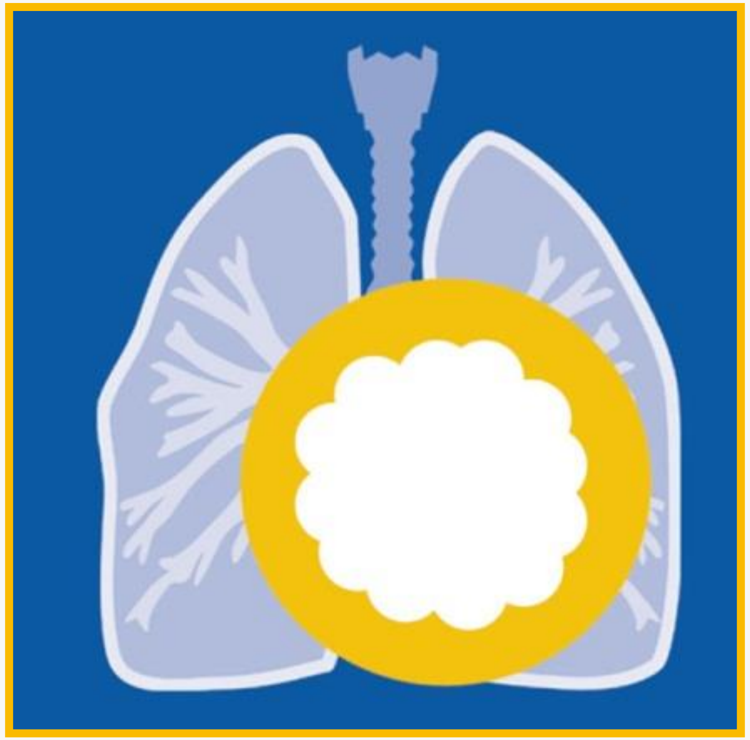
  - Treatment recommendations



GOLD 2017: recommendations to manage stable COPD – pharmacologic treatment

Group B

LAMA + LABA

↑ Persistent symptoms

A long-acting bronchodilator (LABA or LAMA)

→ preferred treatment

GOLD. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2017. Available at: http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/

GOLD 2017 – Pharmacological treatment of stable COPD

Recommendations for GOLD B

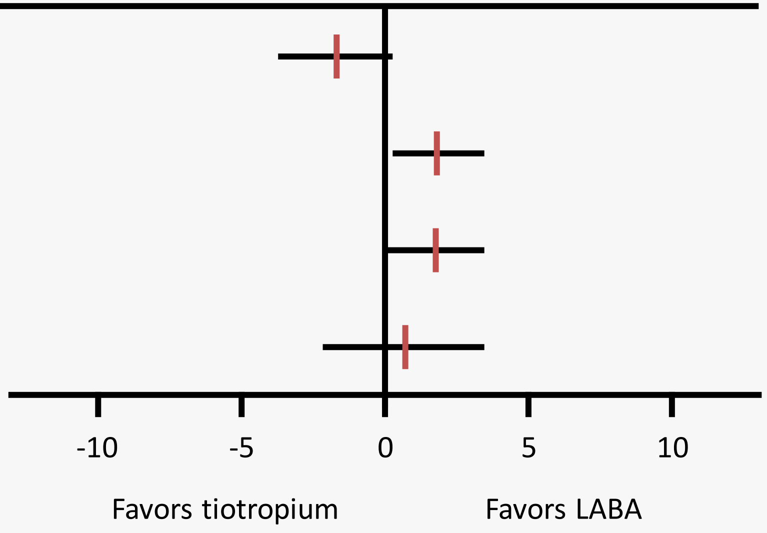
- Initial therapy should consist of a long acting bronchodilator…
- For patients with persistent breathlessness on monotherapy the use of two bronchodilators is recommended
- For patients with severe breathlessness inital therapy with two bronchodilators may be considered

GOLD. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2017. Available at: http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/

LAMA and LABA result in similar QOL improvement

Study or subgroup	Mean difference	SE	Mean difference IV, random, 95% CI
Brusasco 2003 (n=1,207)	–1.4	0.9899	–1.40 (–3.34, 0.54)
Buhl 2011 (n=1,598)	2.1	0.785	2.10 (0.56, 3.64)
Donohue 2010 (n=1,683)	2.1	0.8549	2.10 (0.42, 3.78)
Vogelmeier 2008 (n=847)	1	1.378	1.00 (–1.70, 3.70)

Mean difference IV, random, 95% CI



CI = confidence interval; QOL = quality of life;
SE = standard error

Chong J, et al. Cochrane Database Systemic Rev 2012;9:CD009157

Blinded 12 week comparison of indacaterol and tiotropium in COPD (INTENSITY)

Study design

COPD moderate to severe (mean FEV_1=54%, N=1,598)

Indacaterol 150 µg q.d. | **Tiotropium 18 µg q.d.**

- **12 weeks**

- **Trough FEV_1**
- **FVC**
- **Dyspnea (TDI)**
- **Health status (SGRQ)**

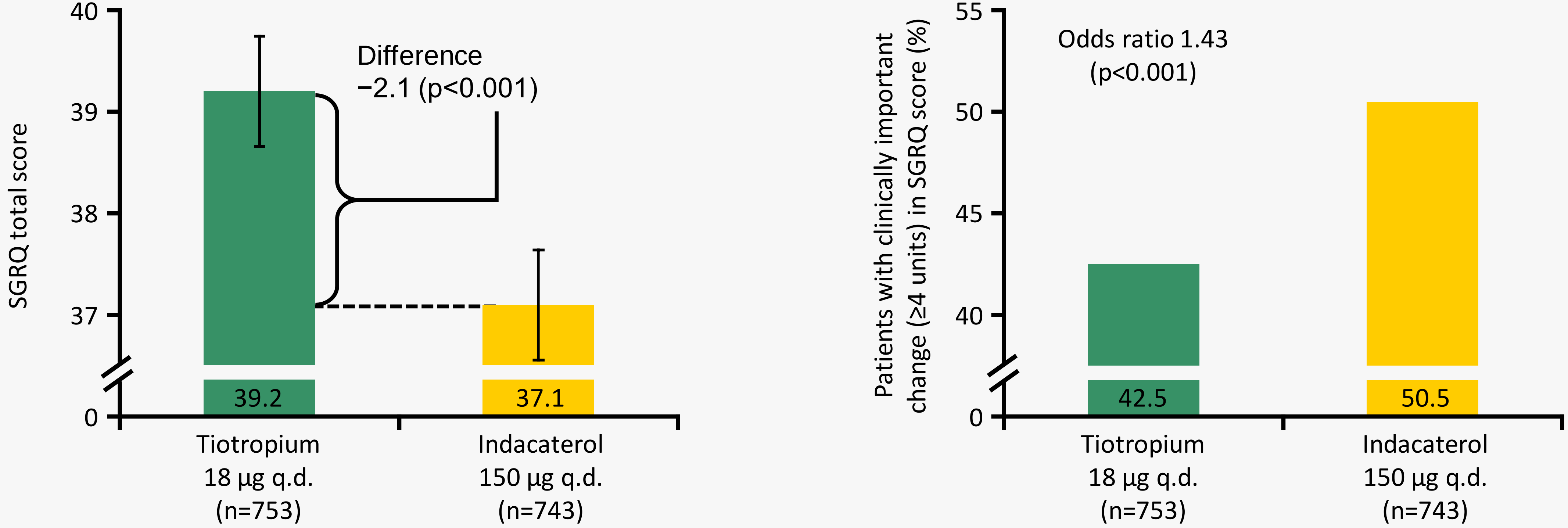
q.d. = once daily; SGRQ = St George's Respiratory Questionnaire; TDI = Transition Dyspnea Index

Buhl R, et al. Eur Respir J 2011;38:797–803

Blinded 12 week comparison of indacaterol and tiotropium in COPD (INTENSITY)

SGRQ

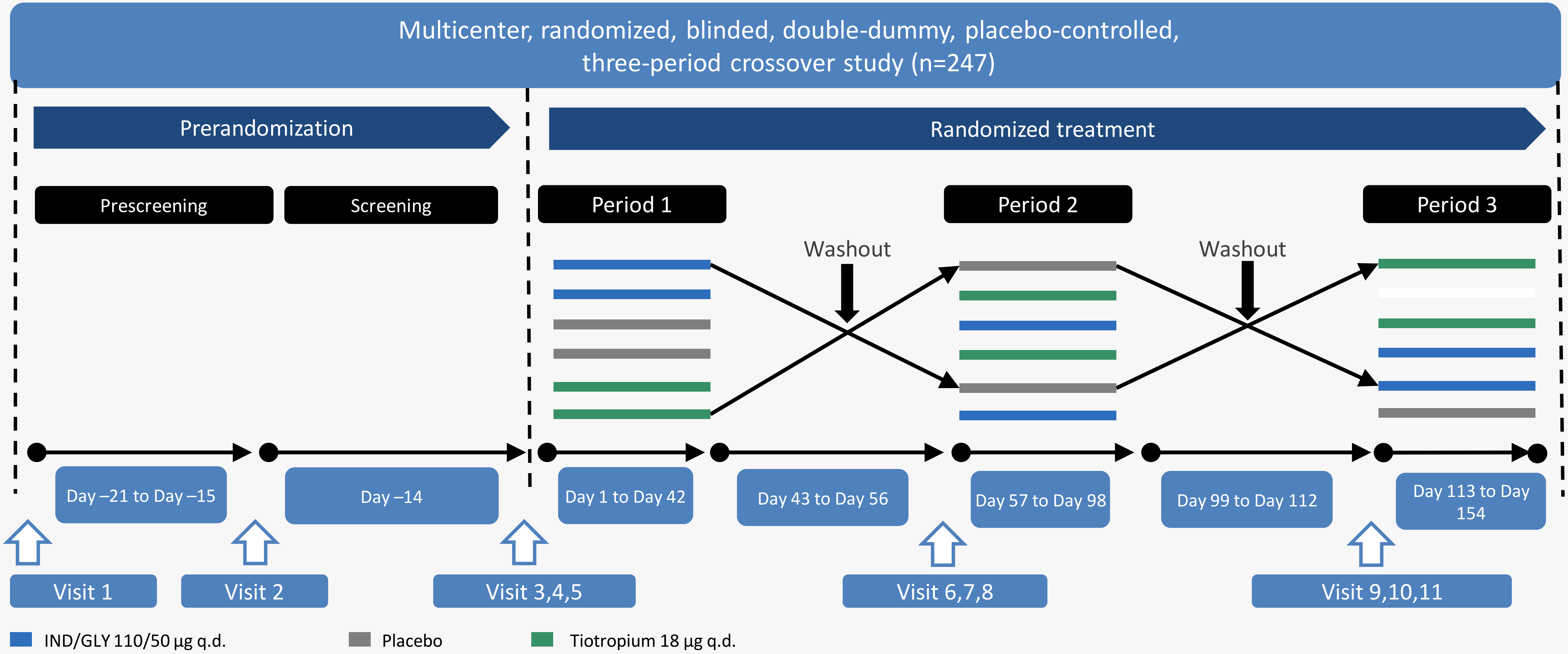
- Changes from baseline (unadjusted means): −5.1 with indacaterol, −3.0 with tiotropium



Adapted from Buhl R, et al. Eur Respir J 2011;38:797–803

Dyspnea with indacaterol/glycopyrronium versus placebo and tiotropium

BLAZE – study design

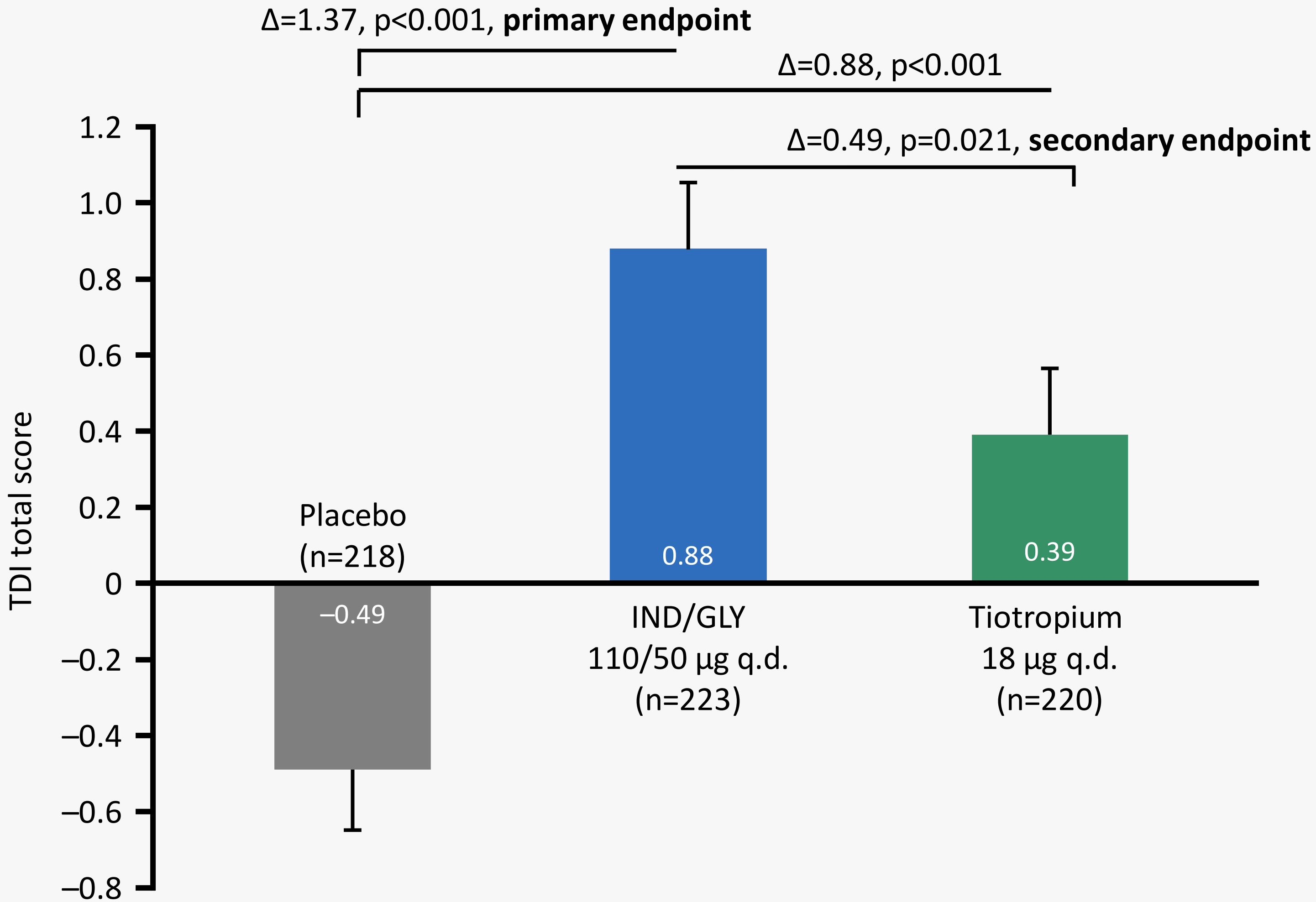


GLY = glycopyrronium; IND = indacaterol

Mahler DA, et al. Eur Respir J 2014;43:1599–609

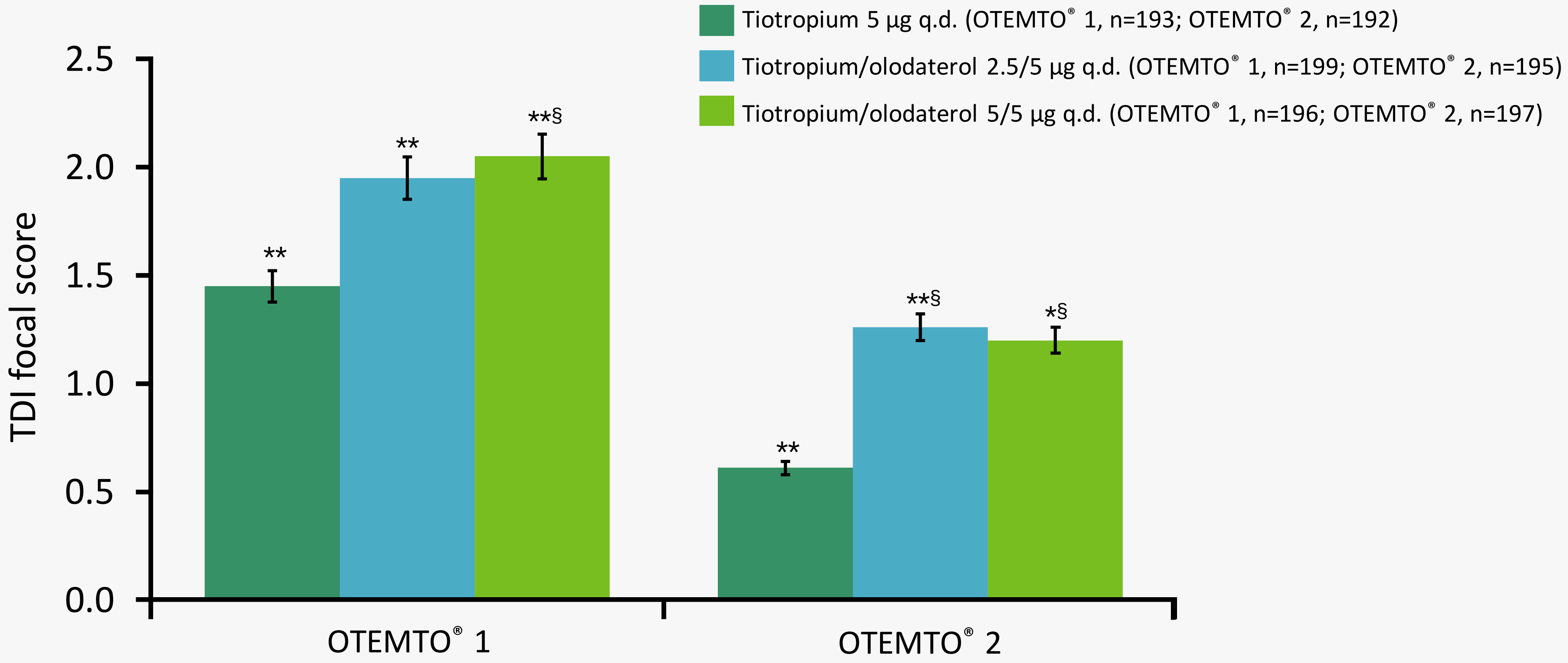
Dyspnea with indacaterol/glycopyrronium versus placebo and tiotropium

BLAZE – TDI after 6 weeks



Mahler DA, et al. Eur Respir J 2014;43:1599–609

Tiotropium/olodaterol: improvements in TDI score versus placebo and tiotropium



Primary endpoints were SGRQ total score, FEV_1 $AUC_{0–3h}$ response and trough FEV_1 response

*p<0.05 vs. placebo; **p<0.0001 vs. placebo; §p<0.001 vs. tiotropium monotherapy

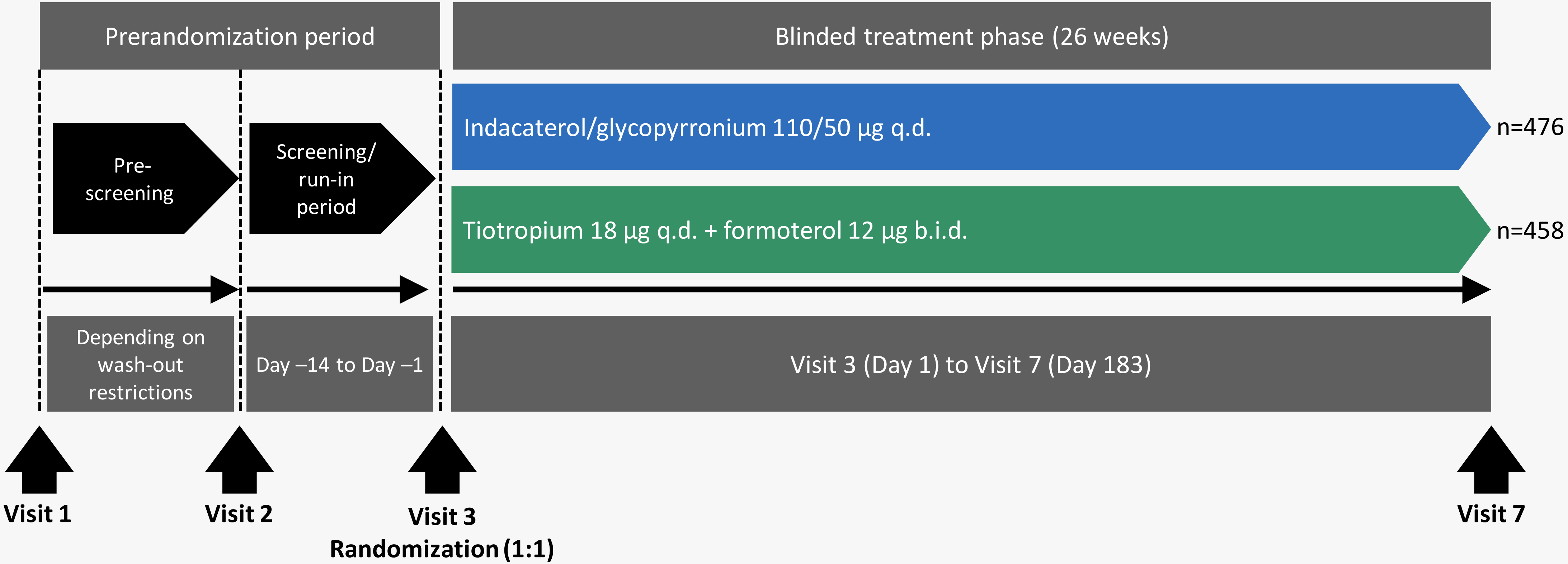
AUC = area under the curve

Singh D, et al. Respir Med 2015;109:1312–9

Indacaterol/glycopyrronium versus tiotropium+formoterol in COPD

QUANTIFY – study design

26-week, multicenter, randomized, blinded, parallel-group, triple-dummy non-inferiority study

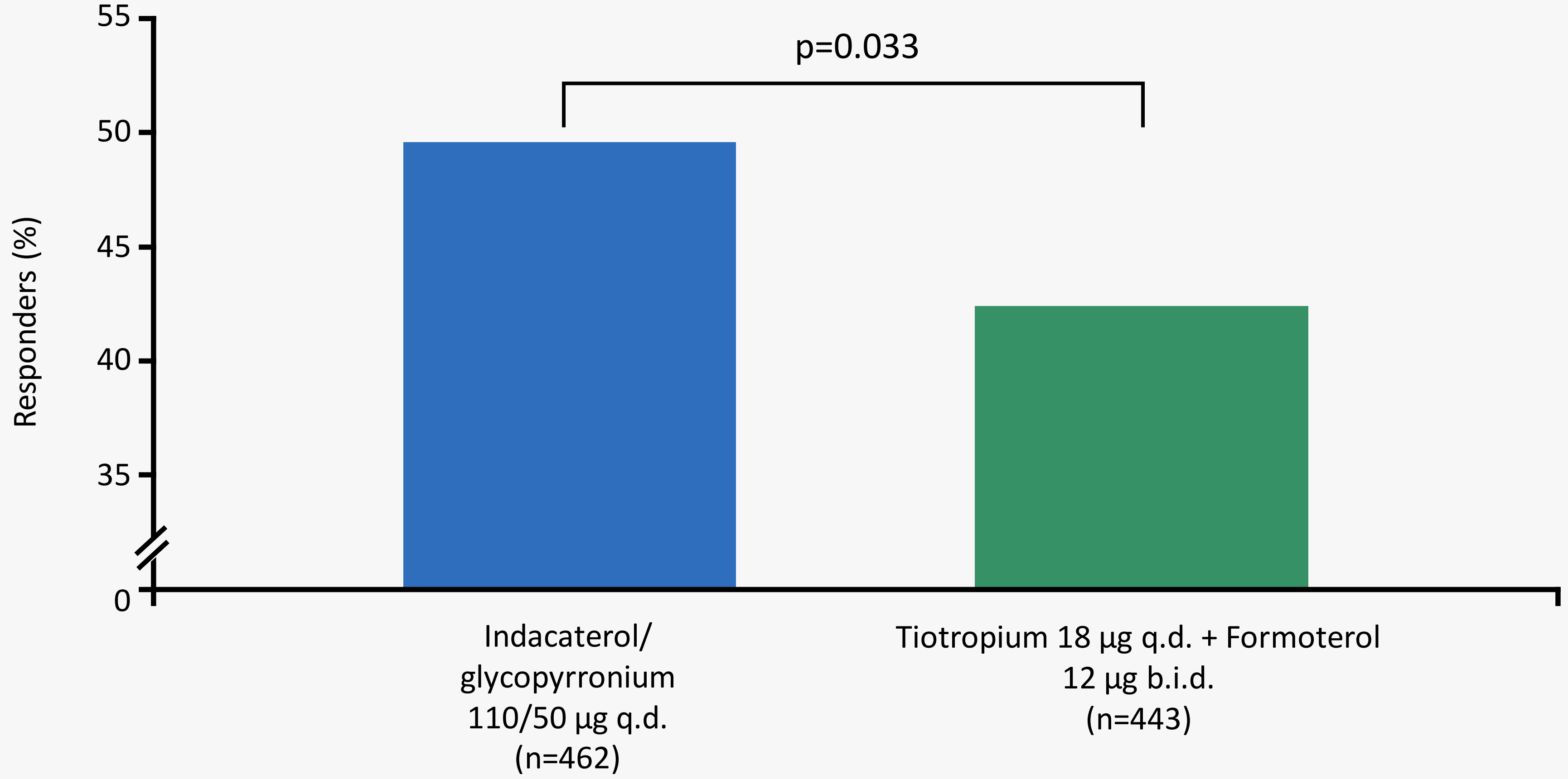


b.i.d. = twice daily

Buhl R, et al. Thorax 2015;70:311–19

Indacaterol/glycopyrronium versus tiotropium+formoterol in COPD

QUANTIFY – TDI responder at Week 26



The primary endpoint was non-inferiority in health-related quality of life, assessed using SGRQ-C

Responders: patients with a clinical improvement of ≥1 unit in TDI
SGRQ-C = St George's Respiratory Questionnaire-COPD

Buhl R, et al. Thorax 2015;70:311–19

LABA/LAMA versus ICS/LABA in COPD patients without frequent exacerbations

Results

LABA/LAMA demonstrated non-inferiority or superiority for many endpoints

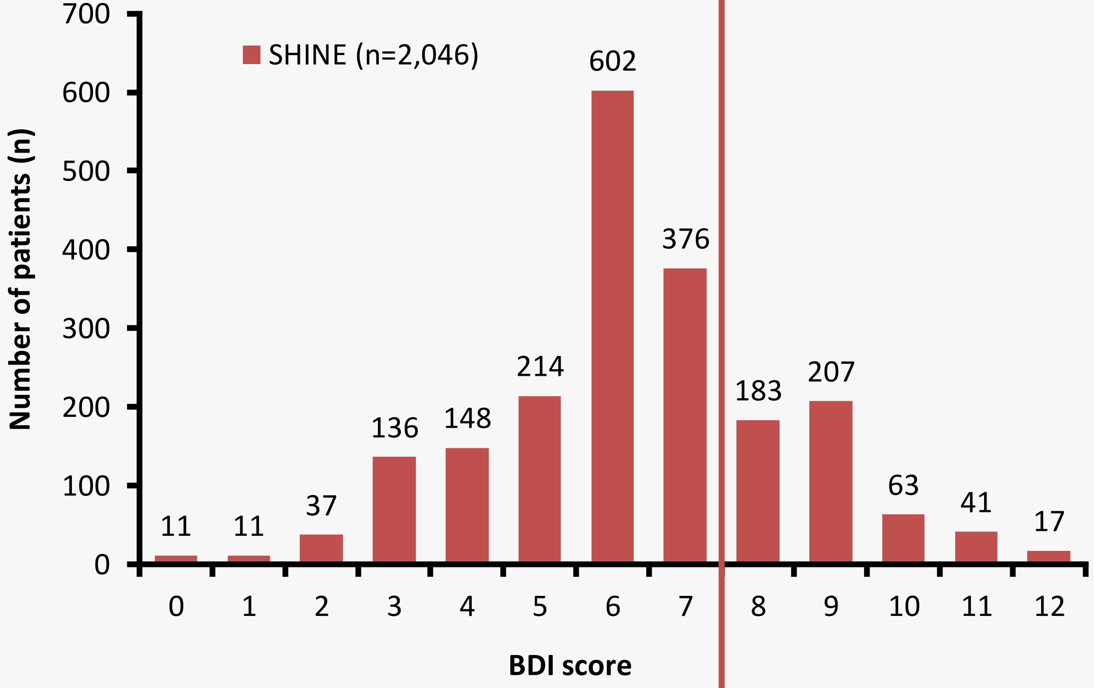
	Treatment arms	Non-inferiority	Superiority
ILLUMINATE[1]	IND/GLY 110/50 µg o.d. (n=258) SFC 50/500 µg b.i.d. (n=264)	• N/A	• **FEV_1 $AUC_{0\text{–}12hrs}$** • TDI focal score
LANTERN[2]	IND/GLY 110/50 µg o.d. (n=372) SFC 50/500 µg b.i.d. (n=369)	• **Trough FEV_1**	• **Trough FEV_1** • Rate of moderate or severe exacerbation • Time to first moderate or severe exacerbation
AFFIRM[3]	Aclidinium/formoterol 400/12 µg b.i.d. (n=423) SFC 50/500 µg b.i.d. (n=414)	• TDI focal score	• **Peak FEV_1**

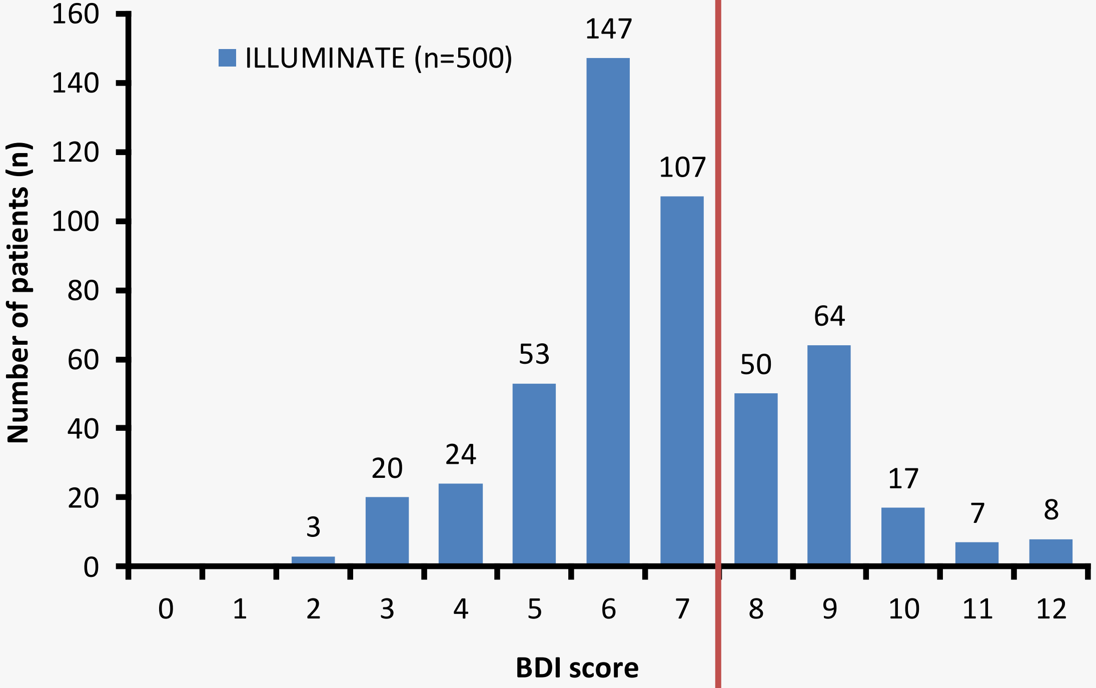
Primary endpoints in **bold**

1. Vogelmeier C, et al. Lancet Respir Med 2013;1:51–60
2. Zhong N, et al. Int J COPD 2015;10:1015–26
3. Vogelmeier C, et al. Eur Respir J 2016;48:1030–39

Efficacy of indacaterol/glycopyrronium in COPD patients with increased dyspnea at daily activities

Post-hoc analysis from SHINE and ILLUMINATE – BDI





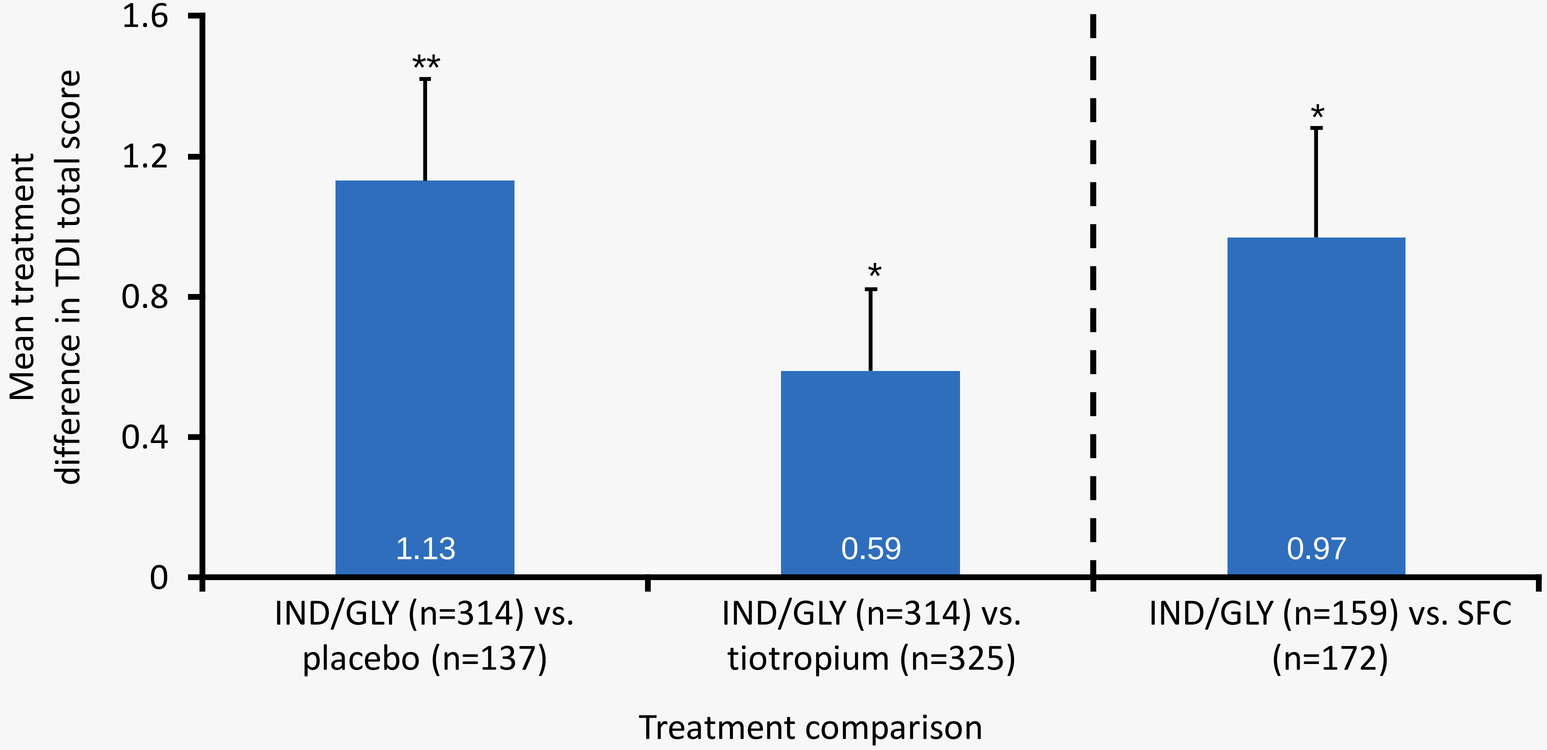
Baseline

BDI = Baseline Dyspnea Index

Mahler DA, et al. Chronic Obstr Pulmon Dis 2016;3:758–68

Efficacy of indacaterol/glycopyrronium in COPD patients with increased dyspnea at daily activities

Post-hoc analysis from SHINE and ILLUMINATE – TDI



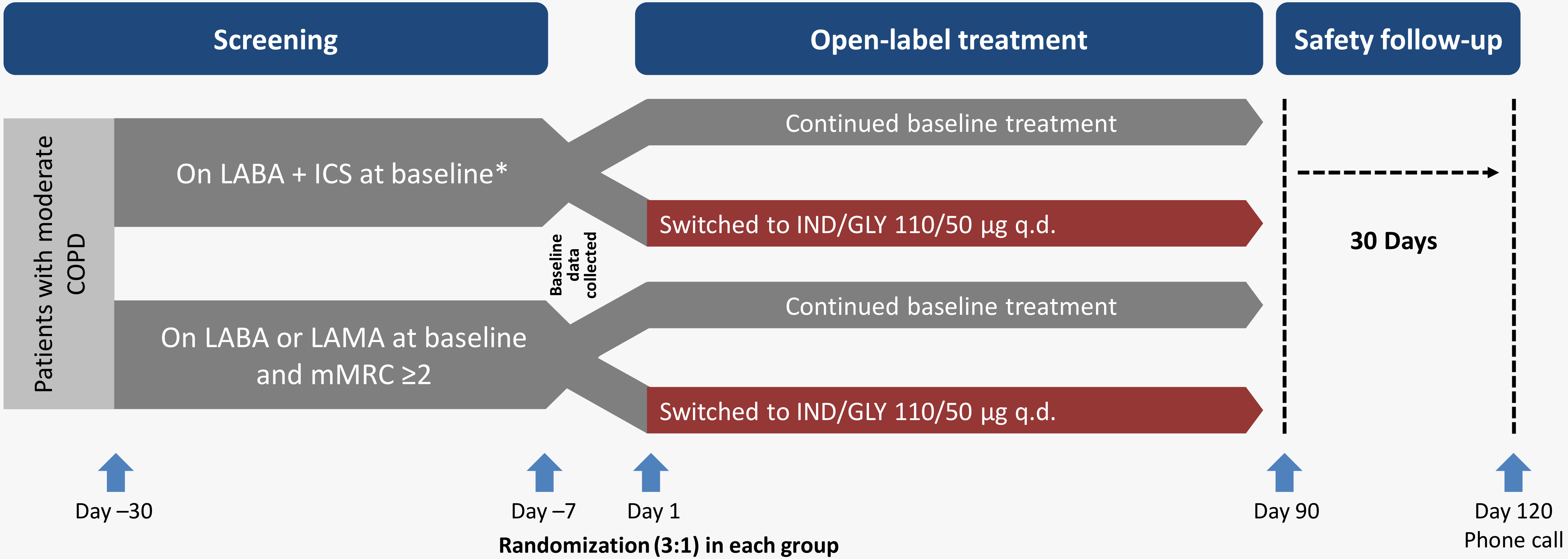
Week 26, patients with a BDI ≤7 at baseline

*p<0.05; **p<0.001
SFC = salmeterol/fluticasone propionate

Mahler DA, et al. Chronic Obstr Pulmon Dis 2016;3:758–68

Efficacy and safety of direct switch to indacaterol/glycopyrronium in patients with moderate COPD: The CRYSTAL open-label randomized trial

Study design



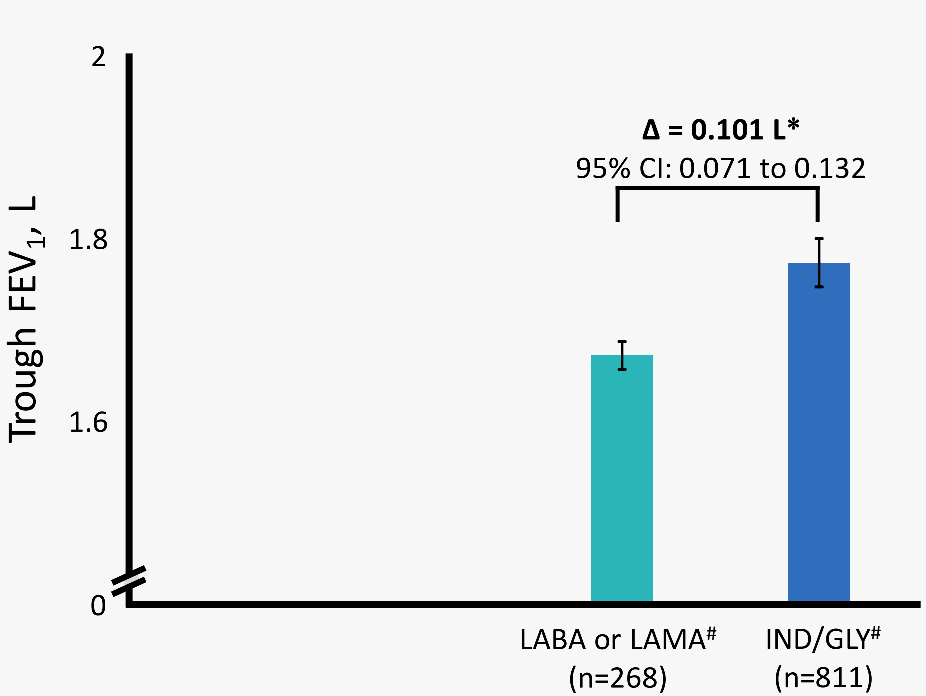
*Free or fixed-dose combination

Vogelmeier C, et al. Respir Res 2017;18:140

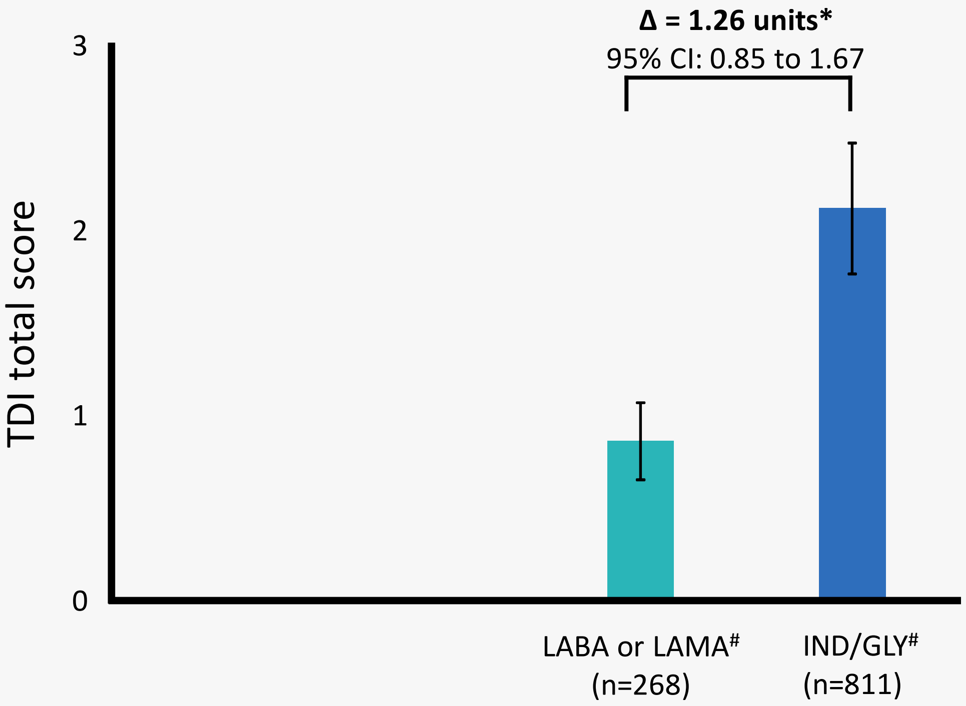
CRYSTAL – co-primary endpoints

Change from baseline in trough FEV_1 and TDI at Week 12 (ITT population)

Change in trough FEV_1



Change in TDI



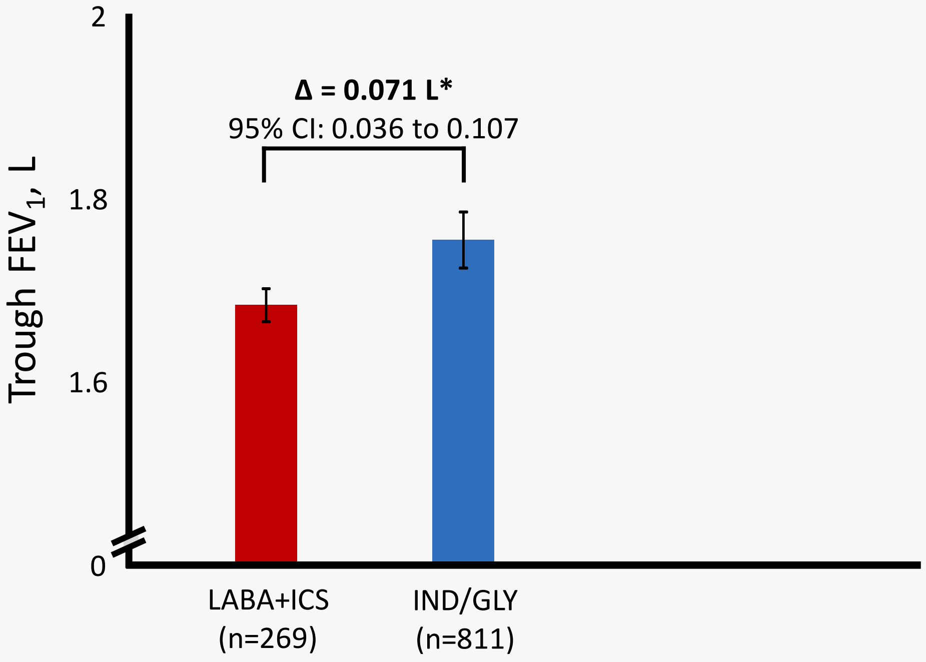
*p<0.0001. #Patients had mMRC ≥2
ITT = intention to treat

Vogelmeier C, et al. Respir Res 2017;18:140

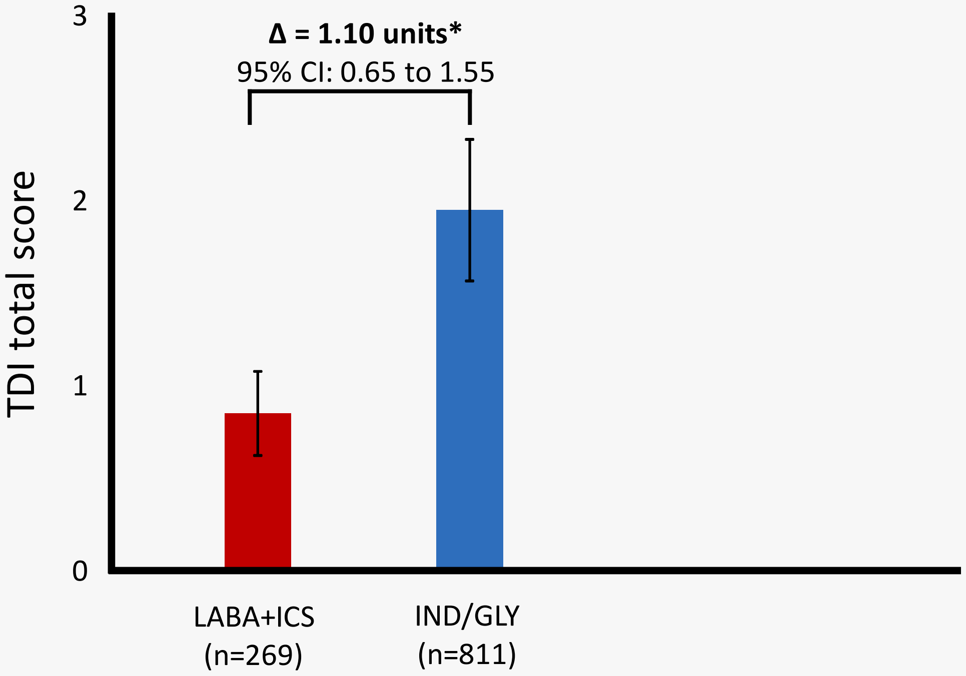
CRYSTAL – co-primary endpoints

Change from baseline in trough FEV_1 and TDI at Week 12 (ITT population)

Change in trough FEV_1



Change in TDI

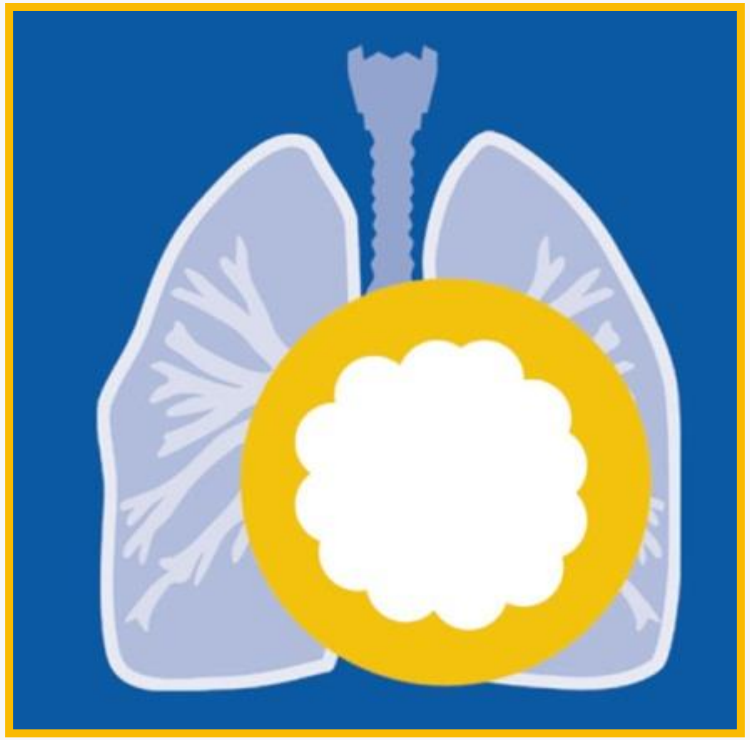


*p<0.0001

Vogelmeier C, et al. Respir Res 2017;18:140

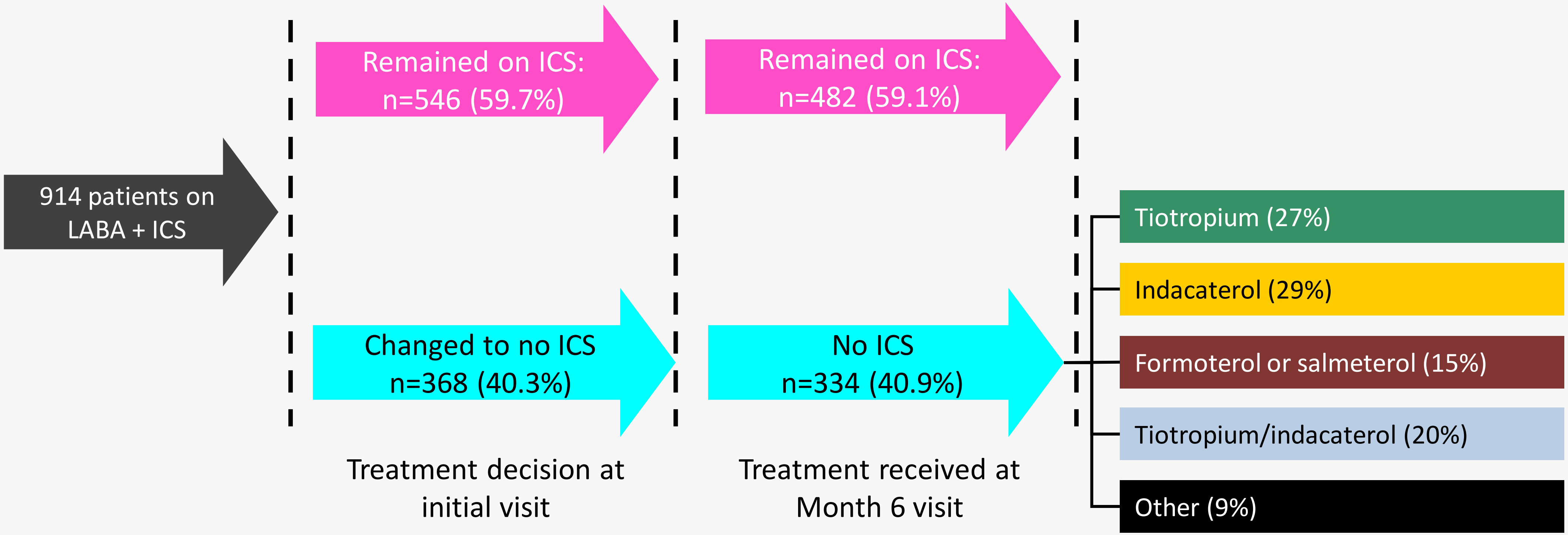
Addressing the needs of patients with a lower exacerbation risk

- GOLD A/B patients
  - Burden of disease
  - Treatment recommendations
  - ICS withdrawal



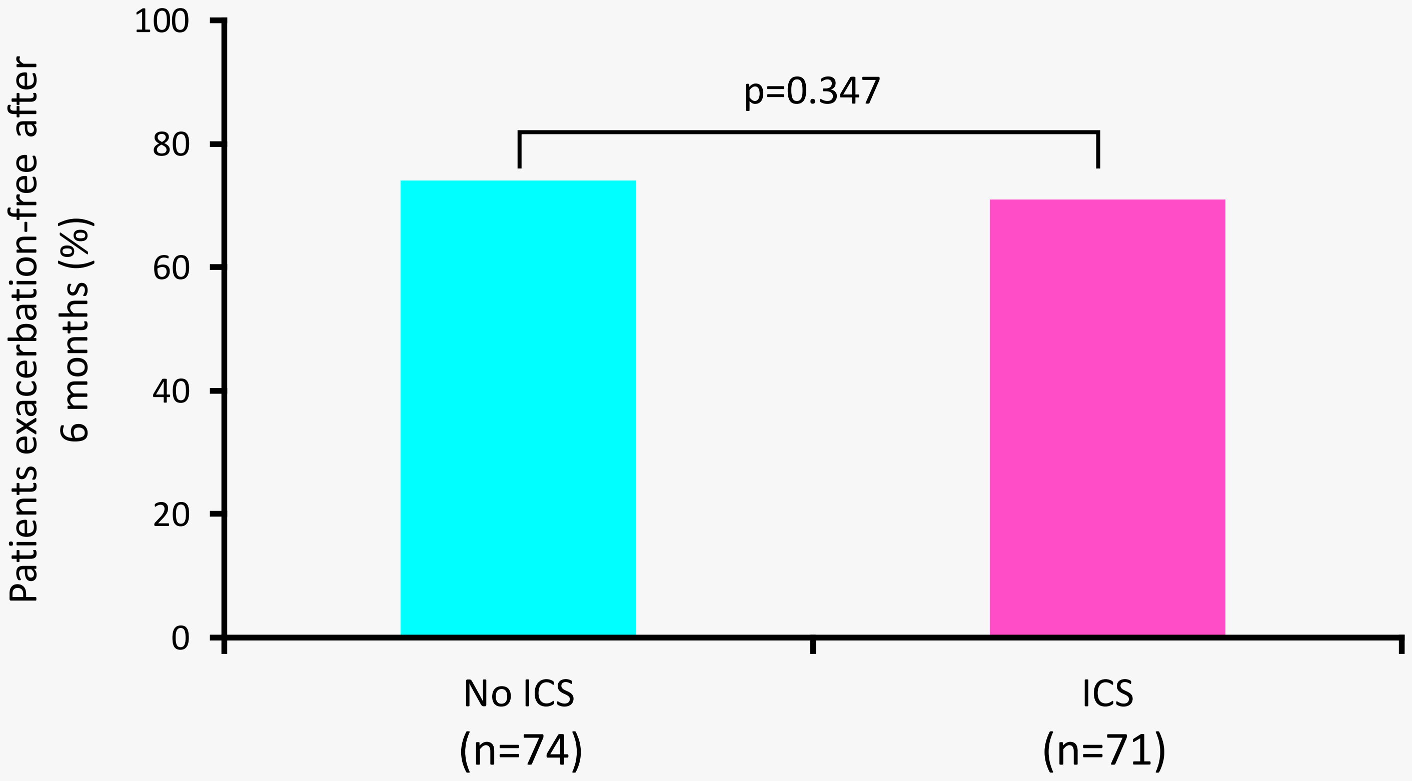
Real life study on the withdrawal of ICS in COPD patients with a low exacerbation risk – OPTIMO: Study design

- Prospective, real-life study: physicians prescribed treatment as they saw fit
  - Aim: to investigate whether withdrawal of ICS in COPD patients at low risk of exacerbation is linked to a deterioration in lung function and symptoms and to a higher frequency of exacerbations.



Rossi A, et al. Respir Res 2014;15:77

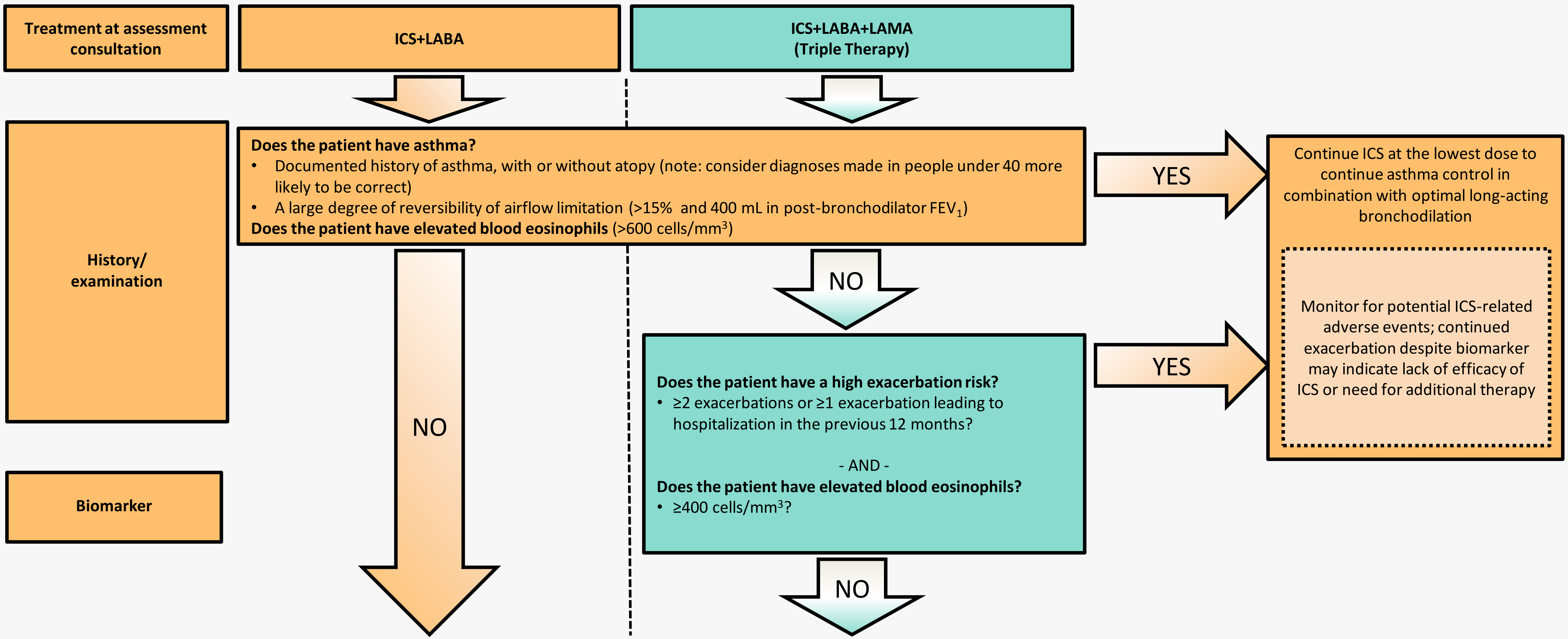
Real life study on the withdrawal of ICS in COPD patients with a low exacerbation risk – OPTIMO: Exacerbation risk



Rossi A, et al. Respir Res 2014;15:77

Evaluation of appropriateness of ICS in COPD and guidance on ICS withdrawal

IPCRG desktop helper (March 2017)



Evaluation of appropriateness of ICS in COPD and guidance on ICS withdrawal

IPCRG desktop helper (March 2017)

Remove ICS or switch to lower-dose ICS in separate inhaler

Low/Medium-dose ICS → stop ICS Switch to LABA/LAMA (optimized bronchodilation)	High-dose ICS → switch to lower-dose ICS in separate inhaler# In combination with LABA/LAMA (optimized bronchodilation)

↓ 4 weeks ↓ 4 weeks → Interim call with patient (approx. 2 weeks) to check compliance and ensure stability

Consultation with monitoring physician including assessment of pulmonary function using spirometry

If stable or improved continue with LABA/LAMA (optimized bronchodilation)	If stable or improved continue with LABA/LAMA (optimized bronchodilation) stop ICS in separate inhaler

→ Patient should be encouraged to contact monitoring physician if any worsening of symptoms or conditions

↓ 6 months

↓ 4 weeks

If stable or improved

continue with LABA/LAMA (optimized bronchodilation)

→ Reassess need for ICS use if:
- Moderate or severe exacerbations
- Airflow limitation worsening (FEV_1 decrease ≥100 mL)
- Optional (blood eosinophil count >400)

↓ 6 months

Follow-up with monitoring physician for full clinical review

See the patient
- twice yearly during the first year of ICS withdrawal,
- followed by an annual review if the patient's COPD is stable and exacerbation-free

#ICS that is not in a combination inhaler

Addressing the needs of patients with a lower exacerbation risk

- GOLD A/B patients
  - Burden of disease – considerable limitations
  - Treatment recommendations – long acting bronchodilators – mono or dual
  - ICS withdrawal – sensible and feasible