Turning Science into Real Life

Roflumilast in Clinical Practice

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Therapy at each stage of COPD

I: Mild	II: Moderate	III: Severe	IV: Very severe
• $FEV_1/FVC < 0.70$ • $FEV_1 \geq 80\%$ pred.	• $FEV_1/FVC < 0.70$ • $50\% \leq FEV_1 < 80\%$ pred.	• $FEV_1/FVC < 0.70$ • $30\% \leq FEV_1 < 50\%$ pred.	• $FEV_1/FVC < 0.70$ • $FEV_1 < 30\%$ pred. *or* $FEV_1 < 50\%$ *plus* chronic respiratory failure

Active reduction of risk factor(s); influenza vaccination

Add Short-acting bronchodilator (when needed)

Add Regular treatment with one or more long-acting bronchodilators (when needed)

Add Rehabilitation

Add Inhaled glucocorticosteroids if repeated exacerbations

Add Long-term O_2 if chronic resp. failure

Consider surgical treatments

GOLD, 2010
www.goldcopd.org

Guideline goals for successful COPD management

Current control

- Relieve symptoms
- Improve exercise tolerance
- Improve health status

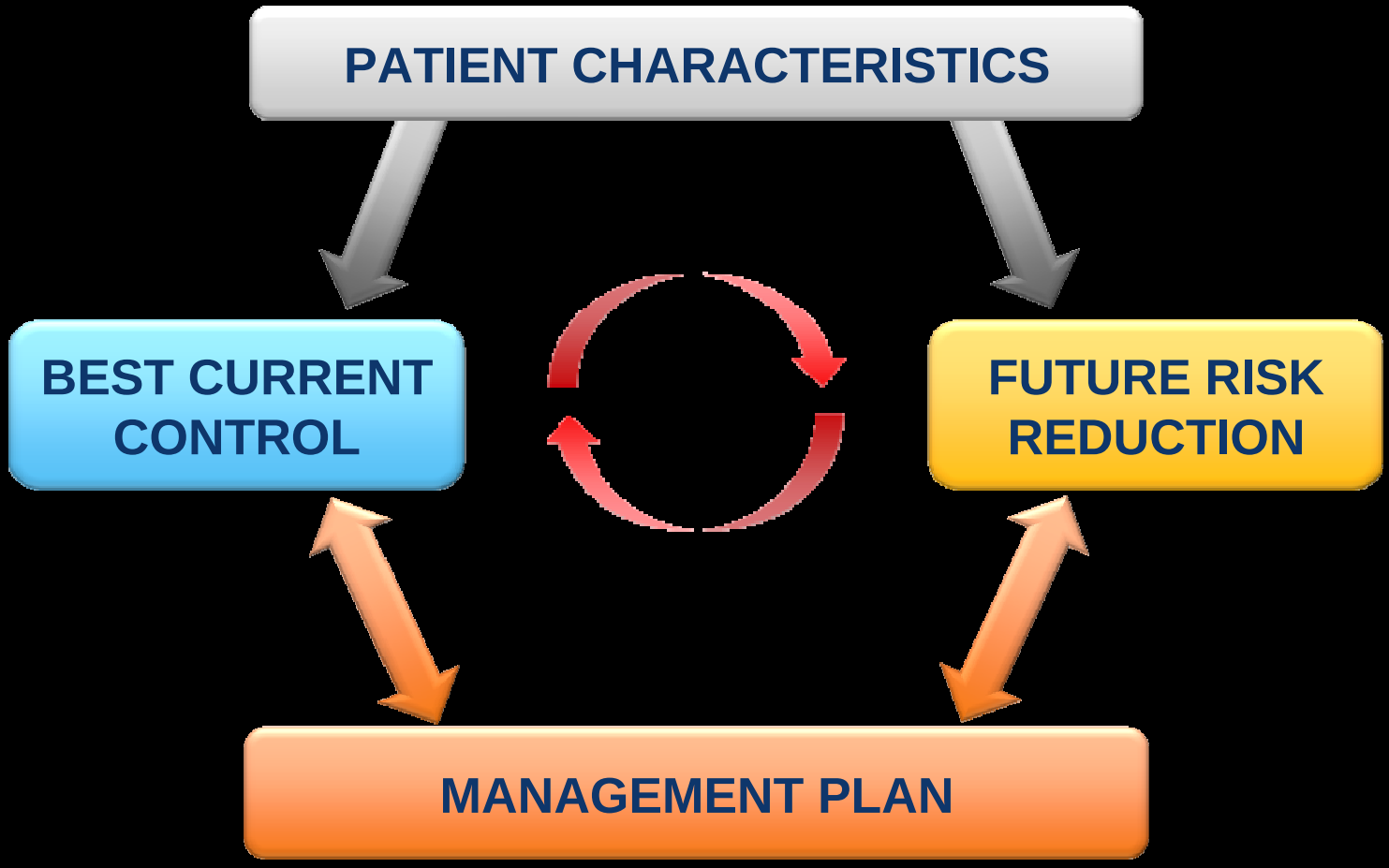
Future risk

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

GOLD Report 2010

Global Initiative for Chronic Obstructive Lung Disease 2010
Available at: http://www.goldcopd.org

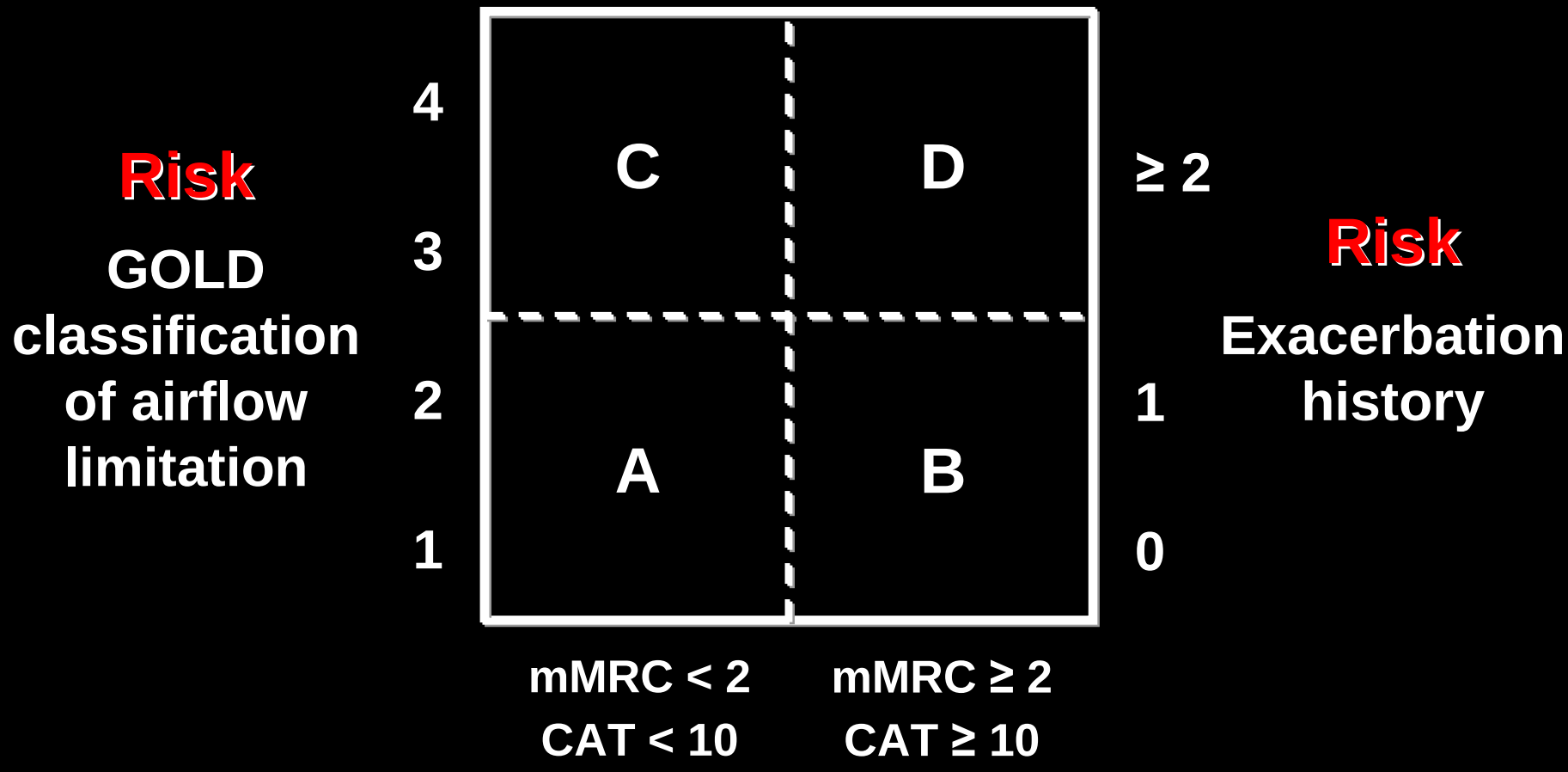
A new perspective on ‘optimal care’ for patients with COPD



Postma, et al. *Prim Care Respir J* 2011; 20:205-209

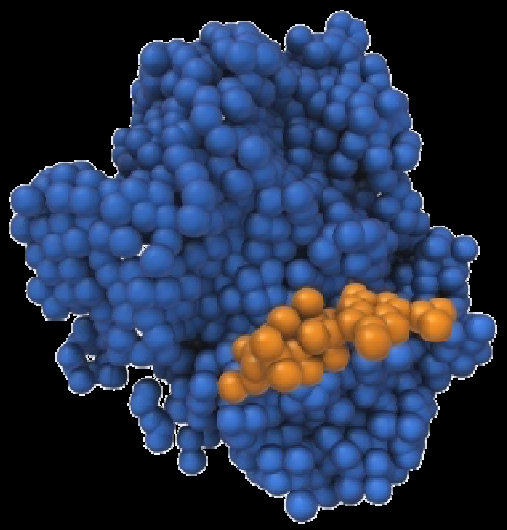
The new GOLD COPD Guidelines

Symptoms, spirometry and future risk



Roflumilast in clinical practice

- Which patients will benefit the most ?



PDE4 inhibition

Reduction of exacerbations by roflumilast

Defining different subsets of COPD patients

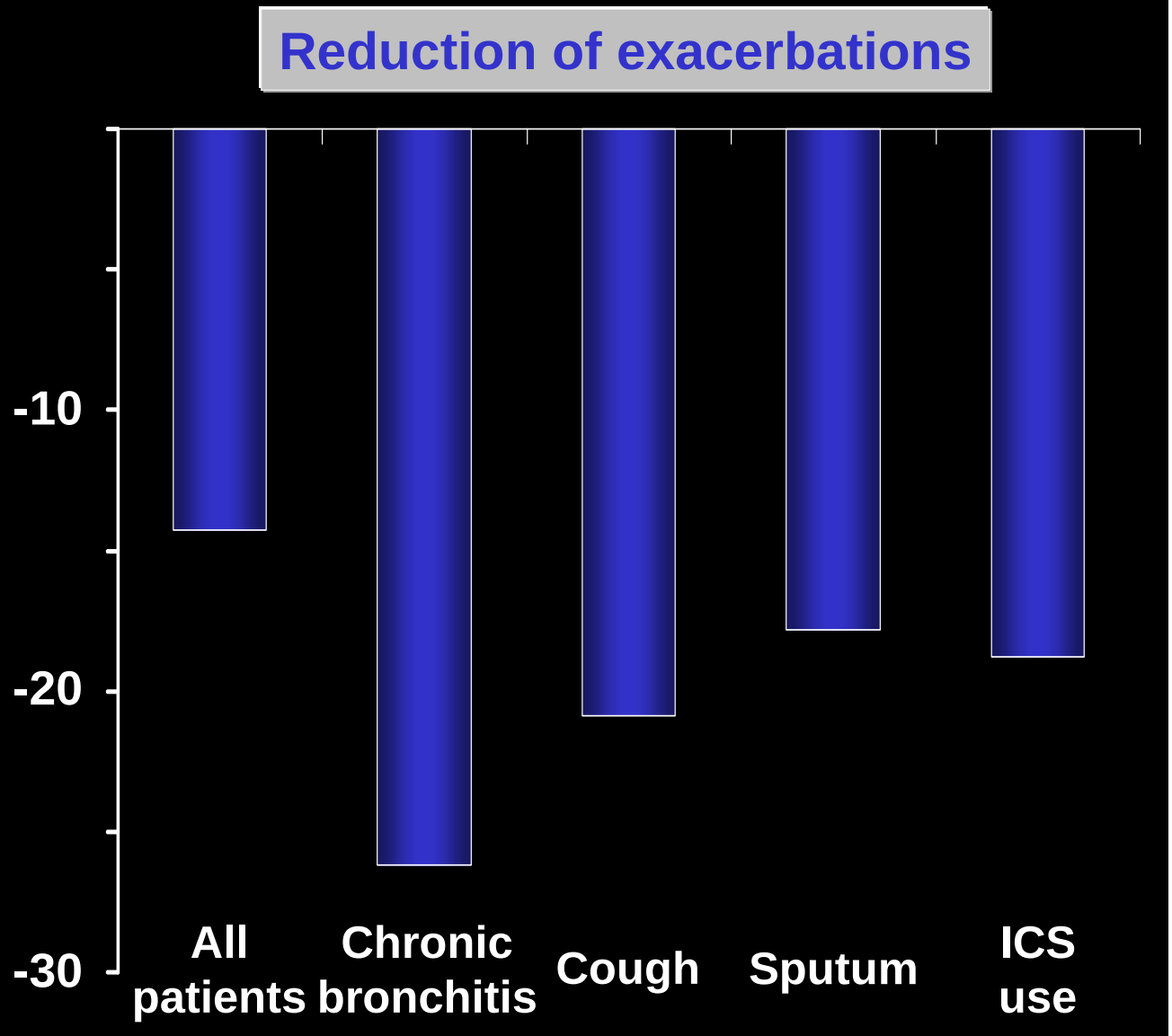
Pooled analysis
2686 COPD patients

- Roflumilast 500 µg / day
- Placebo

1 year

- Exacerbations

Rennard, et al.
Respir Res 2011



The roflumilast phenotype

Roflumilast is indicated for maintenance treatment

- **of severe COPD**
  (FEV_1 post-BD < 50% pred.)
  - **with chronic bronchitis**
  - **and frequent exacerbations**

Roflumilast in clinical practice

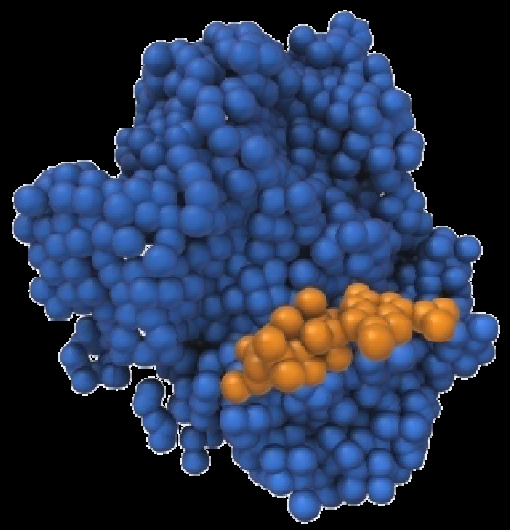
Clinical benefits

- In patients with severe COPD with chronic bronchitis and frequent exacerbations
  - ➢ prevention of exacerbations

Treatment with a PDE4 inhibitor was associated with a reduced likelihood of COPD exacerbation (OR 0.78; 95% CI 0.72 to 0.85)

Chong, et al. Cochrane Database Syst Rev 2011

Roflumilast in clinical practice



PDE4 inhibition

- Which patients will benefit the most ?
- When to prescribe roflumilast ?

ECLIPSE: Frequent exacerbators are a distinct phenotype

Can be identified based on patient recall of previous events

GOLD stage	Exacerbation rate in year 1 (no. / patient)	% of patients who were 'frequent exacerbators'
II	0.85	22
III	1.34	33
IV	2.00	47

Hurst, et al. N Engl J Med 363:1128-1138, 2010

- Ask your patients for any exacerbation (flare-up) treated with antibiotics and/or oral steroids in previous year
- Ask your patients about any hospitalizations due to exacerbations in previous year

If your patient answers **YES** to any of these 2 questions the risk is **5.72 times higher** that this patient will experience 2 or more exacerbations within the next year, compared with the patient who answers NO ($p<0.001$)

The roflumilast patient population

I: Mild	II: Moderate
• $FEV_1/FVC < 0.70$ • $FEV_1 \geq 80\%$ pred.	• $FEV_1/FVC < 0.70$ • $50\% \leq FEV_1 < 80\%$ pred.

Active reduction of risk factor(s); influe

Add Short-acting bronchodilator (wh

Add Regular treatment w
long-acting bronch

Add Rehabilitation

Add

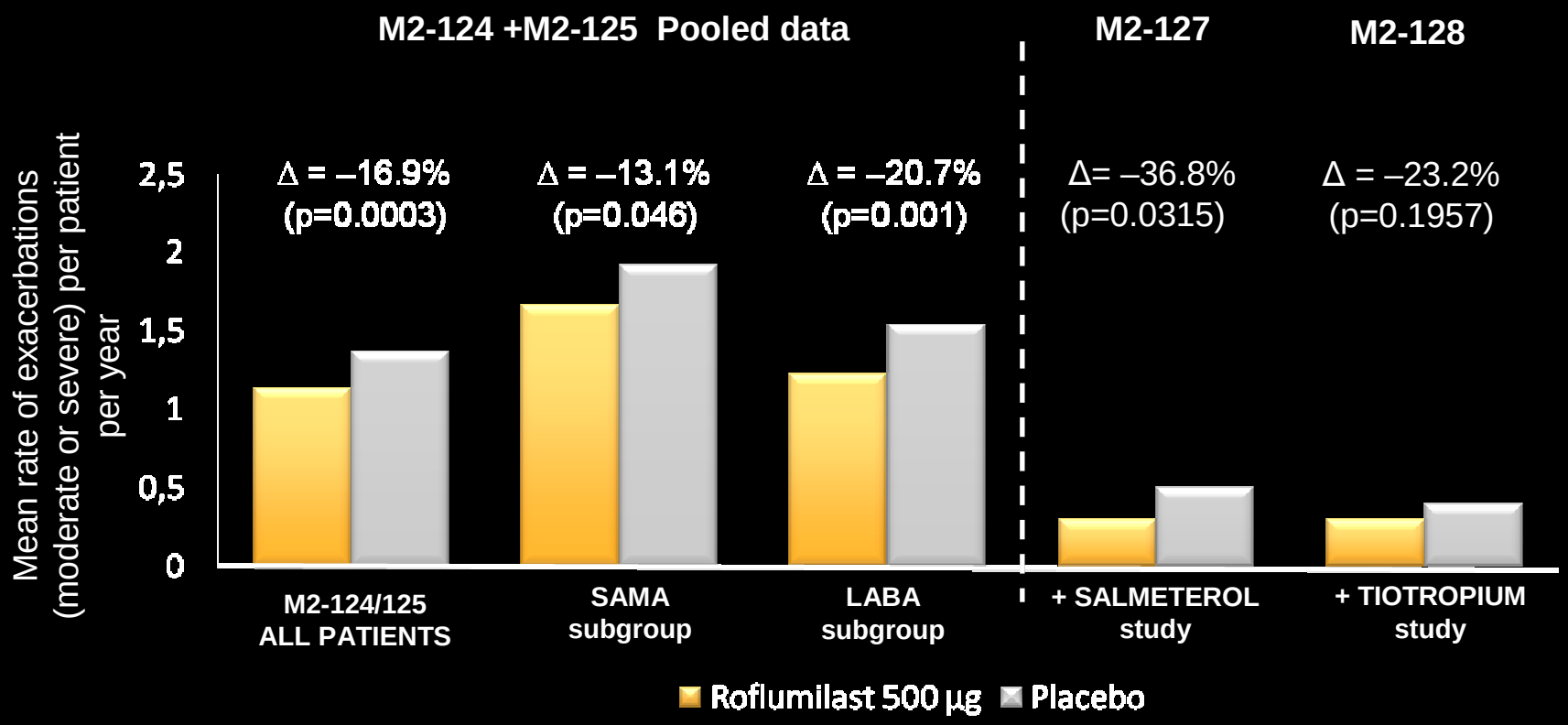
GOLD, 2010
www.goldcopd.com

COPD severity, baseline therapy and exacerbation frequency

GOLD stage	% Patients on long-acting bronchodilators	% Patients on inhaled corticosteroids	Exacerbation rate in year 1 (no./patient)	% of patients who were 'Frequent exacerbators'
II	67	60	0.85	22
III	83	80	1.34	33
IV	86	86	2.00	47

Hurst, et al. N Engl J Med
363:1128-1138, 2010

Roflumilast reduced exacerbations when added to bronchodilators

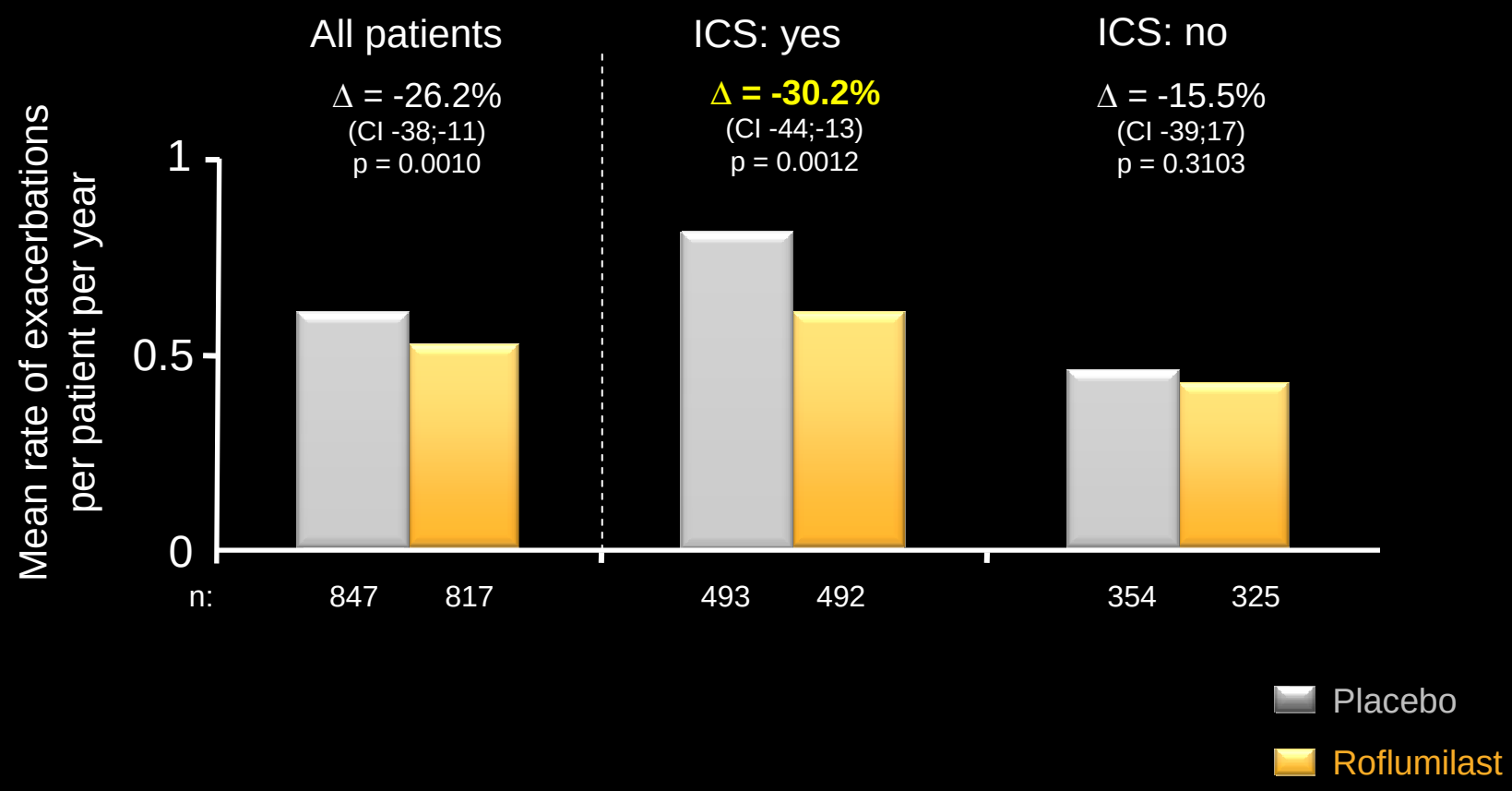


Rabe KF. Br J Pharm **2011**;163:53-67

LABA = Long-acting β_2-agonist
SAMA = Short-acting muscarinic antagonist

Roflumilast reduced exacerbation rate when added to ICS

M2-111 and M2-112 pooled post hoc analysis of sub-group with chronic bronchitis +/- ICS



Rennard SI, Calverley PMA, Goehring UM, et al. *Respiratory Research* **2011**; 12: 18.

ICS = Inhaled corticosteroids

Roflumilast in clinical practice

Co-medication

Roflumilast *plus*	Effects
LABAs	• additive
Tiotropium	• additive
ICS	• potentially additive
Theophylline	• not recommended • short-term during exacerbations unproblematic
SABAs, ipratropium	• rescue medication in clinical trials

Calverley, et al. COPD 7, 2010
Bohmer, et al. VKLIPHA 2010

Roflumilast in clinical practice

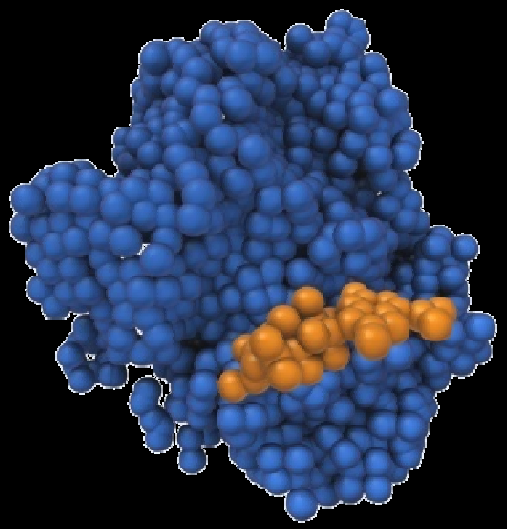
Clinical benefits

- In patients with severe COPD with chronic bronchitis and frequent exacerbations
  - ➢ prevention of exacerbations
- Add-on to bronchodilatory maintenance treatment with additive effects

Chong, et al. Cochrane Database Syst Rev 2011

Calverley, et al. Lancet 2009; 374:685–9
Fabbri, et al. Lancet 2009;374:695–703

Roflumilast in clinical practice



PDE4 inhibition

- Which patients will benefit the most ?
- When to prescribe roflumilast ?
- The patient perspective

What are the risks associated with chronic cough and sputum?

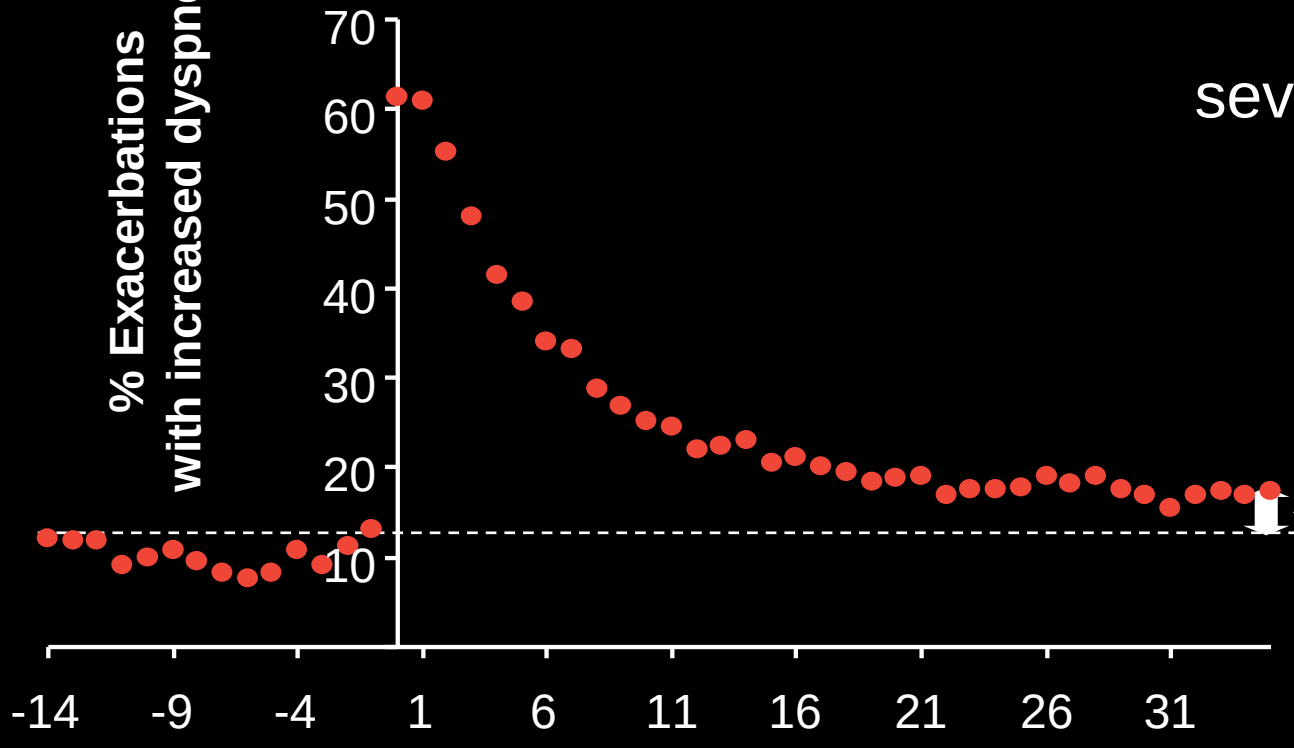
- **COPD patients with cough and sputum are more likely to have**
  - **Respiratory infections**
  - **Increased airway inflammation**
  - **Frequent exacerbations**
  - **Steeper decline in FEV_1**
  - **Increased risk of mortality**

Burgel PR, Nesme-Meyer P, Chanez P, et al. *Chest* **2009**;135:975-982
Saetta M, Baraldo S, Corbino L, et al. *Am J Respir Crit Care Med* **1999**;160:711-717. Guerra S, Sherrill DL, Venker C, et al. *Thorax* **2009**;64:894–900
Vestbo J, Prescott E, Lange P, et al. *Am J Respir Crit Care Med* **1996**;153:1530-1535. Lundbäck B et al. *J COPD* **2009**;6:263-271

Prolonged recovery of symptoms after a COPD exacerbation

Dyspnea

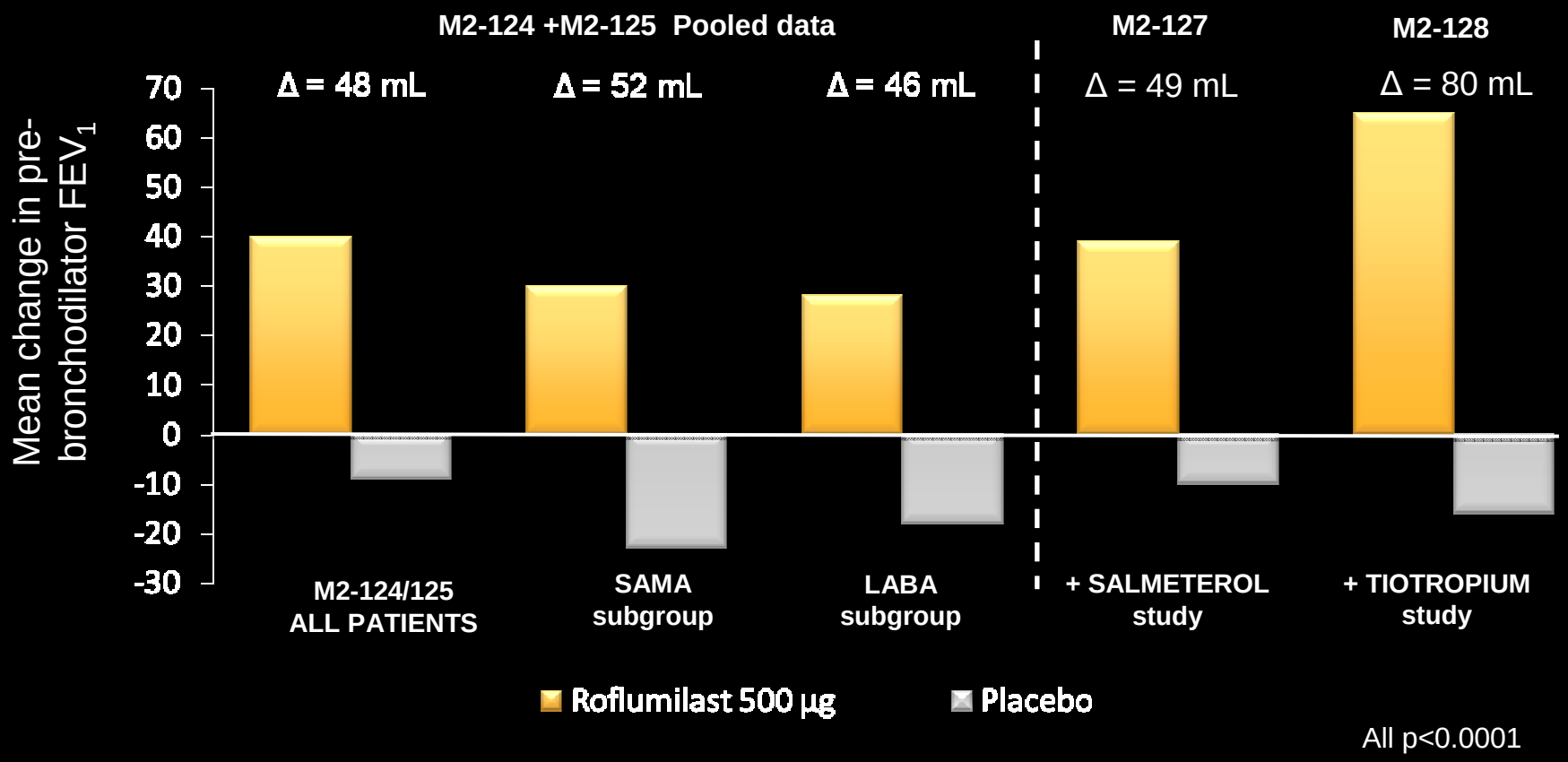
Prospective study, n=101
504 moderate to
severe exacerbations



No return to baseline:
At day 35: 20%
At day 91: 4.6%

Seemungal, et al. AJRCCM 2000; 161:1608-1613

Roflumilast improved lung function when added to bronchodilators



All p<0.0001

Rabe KF. *Br J Pharm* **2011**;163:53-67.

LABA = Long-acting β_2-agonist
SAMA = Short-acting muscarinic antagonist

Roflumilast in clinical practice

Clinical benefits

- In patients with severe COPD with chronic bronchitis and frequent exacerbations
  - ➢ prevention of exacerbations
  - ➢ improvement of lun ion
- Add-on t

Treatment with a PDE4 inhibitor was associated with a significant improvement in FEV1 (45.59 mL; 95% CI 39.15 to 52.03), regardless of COPD severity or concomitant COPD treatment

Chong, e Database Syst Rev

Calverley, et al. Lancet 2009; 374:685–9
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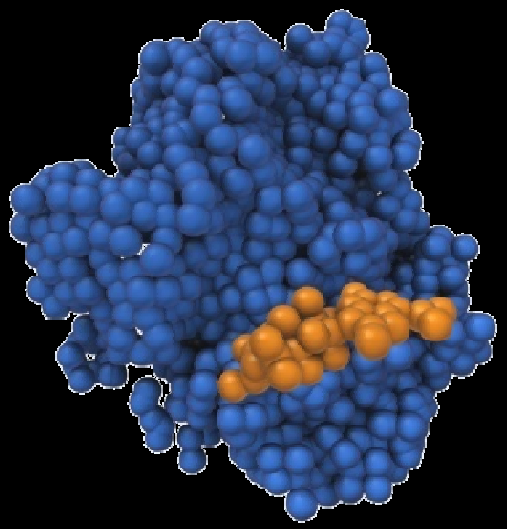
Roflumilast in clinical practice



PDE4 inhibition

- Which patients will benefit the most ?
- When to prescribe roflumilast ?
- The patient perspective
- Roflumilast on target

Therapy at each stage of COPD

I: Mild	II: Moderate	III: Severe	IV: Very severe
• $FEV_1/FVC < 0.70$ • $FEV_1 \geq 80\%$ pred.	• $FEV_1/FVC < 0.70$ • $50\% \leq FEV_1 < 80\%$ pred.	• $FEV_1/FVC < 0.70$ • $30\% \leq FEV_1 < 50\%$ pred.	• $FEV_1/FVC < 0.70$ • $FEV_1 < 30\%$ pred. *or*

Active reduction of risk fact

Add Short-a

Phosphodiesterase-4 inhibitors: In patients with Stage III: Severe COPD or Stage IV: Very Severe COPD and a history of exacerbations and chronic bronchitis, the phosphodiesterase-4 inhibitor, roflumilast, reduces exacerbations treated with oral glucocorticosteroids. These effects are also seen when roflumilast is added to long-acting bronchodilators; there are no comparison studies with inhaled glucocorticosteroids.

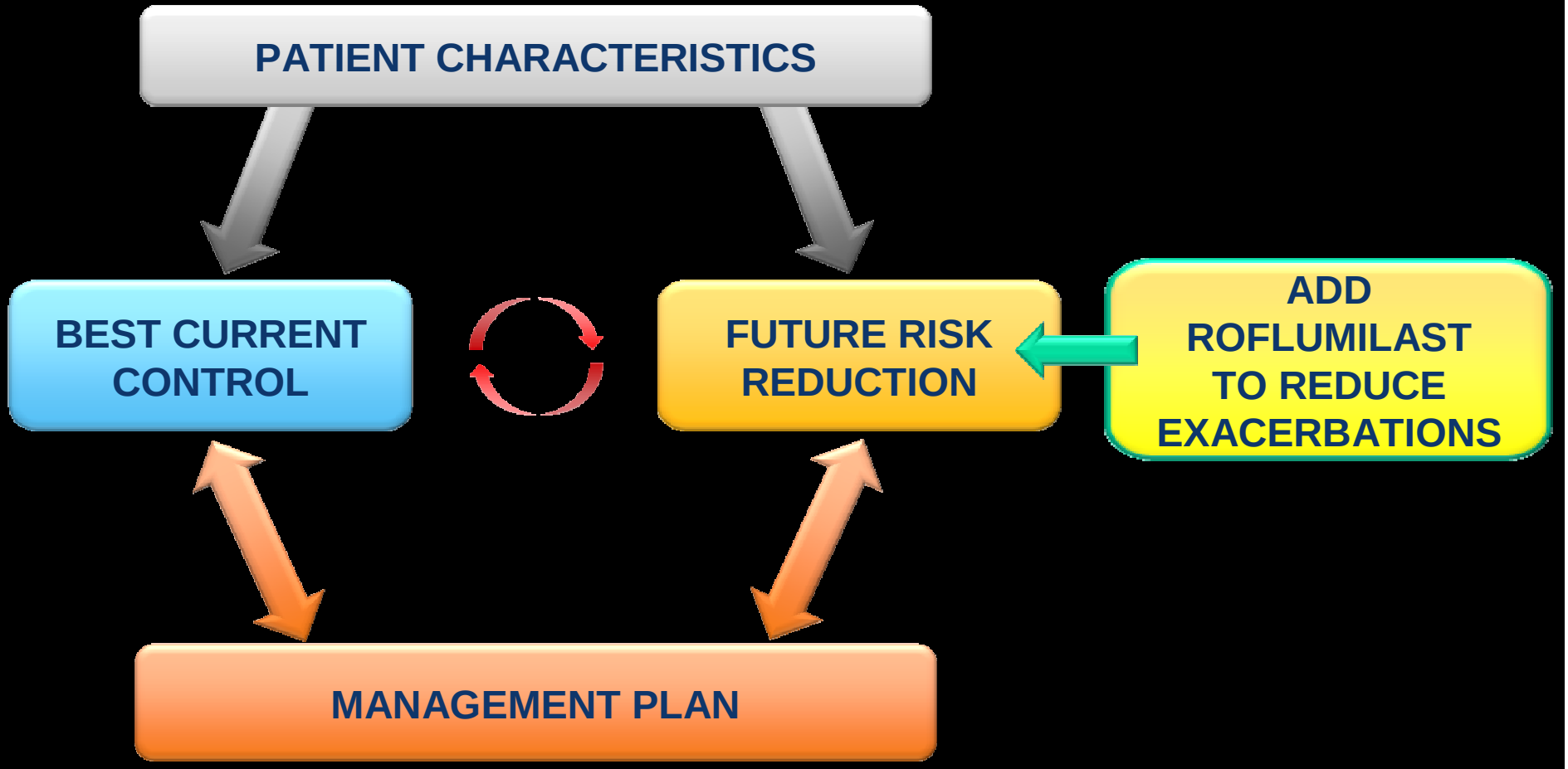
needed)

Add Inhaled glucocorticosteroids if repeated exacerbations

Add Long-term O_2 if chronic resp. failure
Consider surgical treatments

GOLD, 2010
www.goldcopd.org

A new perspective on ‘optimal care’ for patients with COPD

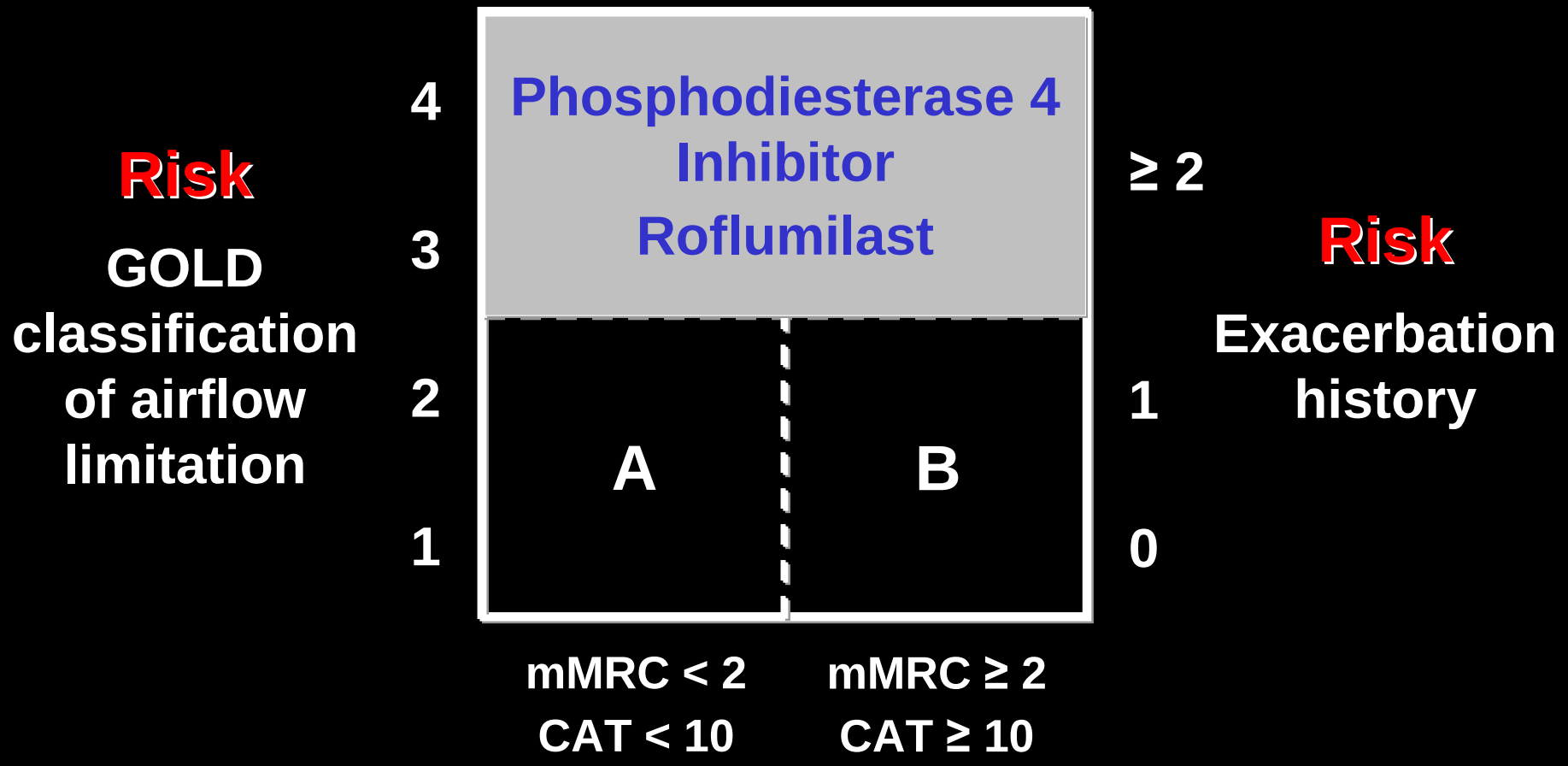


Postma, et al. Prim Care Respir J 2011; 20:205-209

GOLD, 2010
www.goldcopd.org

The new GOLD COPD Guidelines

Symptoms, spirometry and future risk



Roflumilast in clinical practice

- Recommended dose 500 µg / day orally
- Once daily dosing
  - at any time of the day
  - but always at the same time of the day
  - independent of meals

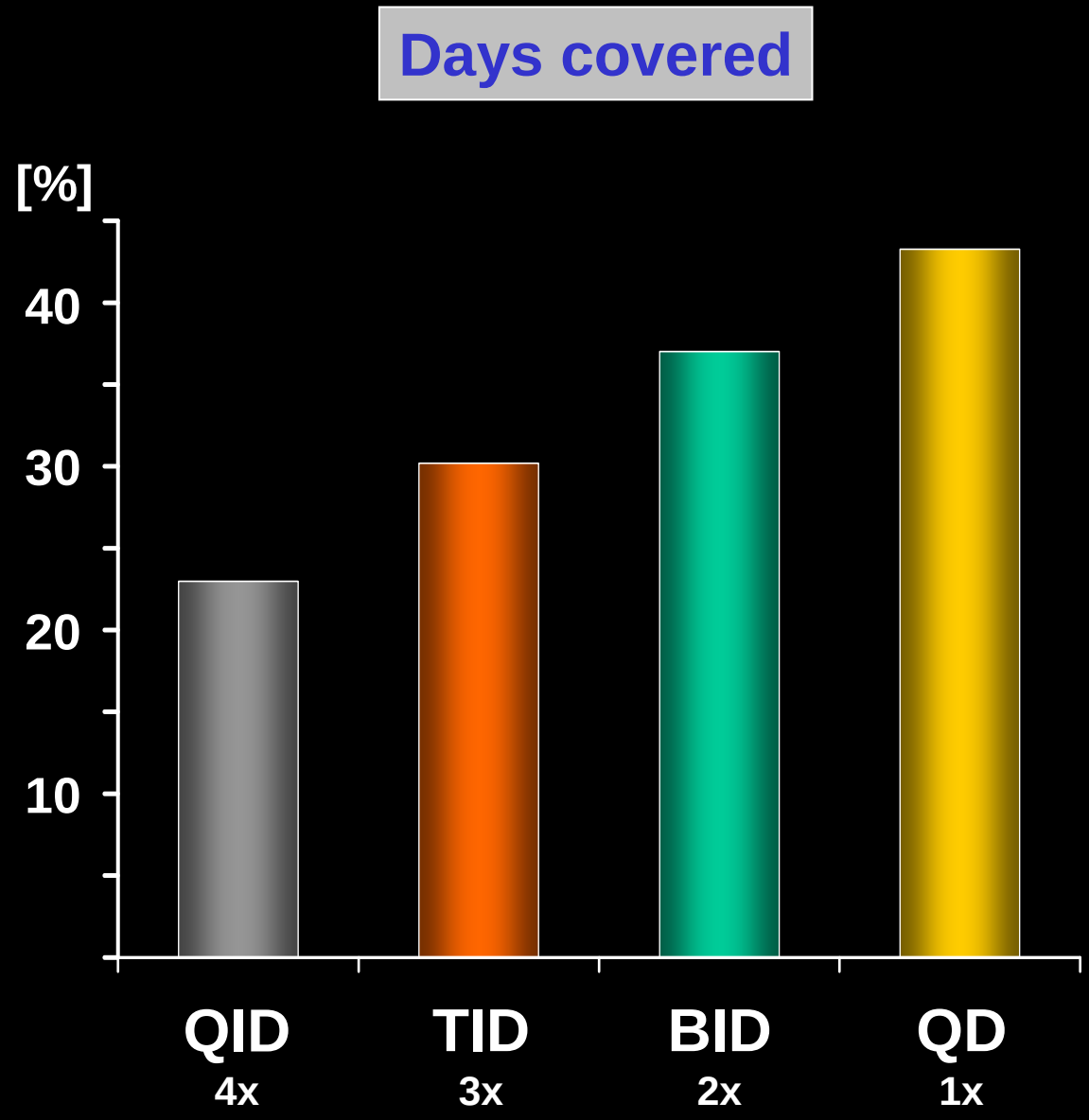
Dosing frequency and adherence in COPD

55 076 COPD patients
1999 - 2006

- Dosing frequency of first COPD drug claim after diagnosis

12 months

Proportion of days covered



Toy, et al. Respir Med 2010

Roflumilast in clinical practice

- Recommended dose 500 µg / day orally
- Once daily dosing
  - at any time of the day
  - but always at the same time of the day
  - independent of meals
- No dose adaptation in elderly patients, smokers, and renal insufficiency
- Contraindicated in patients with moderate and severe liver dysfunction

Incidence of AEs (≥ 2.5%)*

Independent of investigator causality assessments (1/2)

	M2-124		M2-125	
	Roflumilast 500µg (n=769)	**Placebo** (n=755)	**Roflumilast 500µg** (n=778)	**Placebo** (n=790)
COPD	**9.1 %**	**10.9 %**	**11.2 %**	**15.4 %**
Diarrhoea	**8.2 %**	**3.4 %**	**8.6 %**	**2.9 %**
Weight decrease	**12.0 %**	**3.2 %**	**8.4 %**	**2.5 %**
Nasopharyngitis	**7.4 %**	**6.6 %**	**4.5 %**	**5.9 %**
Upper Respiratory Tract Infection	**2.1 %**	**2.8 %**	**4.2 %**	**4.8 %**
Headache	**3.4 %**	**2.3 %**	**3.2 %**	**1.0 %**
Pneumonia	**2.2 %**	**2.0 %**	**3.2 %**	**2.0 %**

descending order of M2-125

Calverley et al., Lancet 2009;374:685–694

Incidence of AEs (≥ 2.5%)*

Independent of investigator causality assessments (2/2)

	M2-124		M2-125	
	Roflumilast 500µg (n=769)	Placebo (n=755)	Roflumilast 500µg (n=778)	Placebo (n=790)
Back Pain	3.5 %	2.9 %	3.0 %	1.6 %
Bronchitis	4.6 %	5.3 %	2.7 %	3.0 %
Nausea	5.3 %	2.0 %	2.7 %	1.9 %
Hypertension	2.6 %	3.7 %	2.3 %	2.5 %
Insomnia	2.5 %	1.1 %	2.3 %	1.5 %
Decreased Appetite	2.7 %	0.3 %	1.9 %	0.6 %
Influenza	3.5 %	2.4 %	1.5 %	2.5 %

**descending order of M2-125*

Calverley et al., Lancet 2009;374:685–694

Roflumilast in clinical practice

- Recommended dose 500 µg / day orally
- Once daily dosing
  - at any time of the day
  - but always at the same time of the day
  - independent of meals
- No dose adaptation in elderly patients, smokers, and renal insufficiency
- Contraindicated in patients with moderate and severe liver dysfunction
- Roflumilast is not a bronchodilator
  - no immediate onset of action

Roflumilast in clinical practice

- Inhibition of COPD-specific inflammatory processes
- In patients with severe and very severe COPD, chronic bronchitis and frequent exacerbations
  - ➢ improvement of lung function
  - ➢ prevention of exacerbations
- Effects additive to bronchodilators