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NOVEMBRE
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OTTICA
RESPIRO
IL PAZIENTE AL CENTRO
VERONA 2018
HOTEL LEON D'ORO

UNIVERSITAS STUDIORUM MUTINENSIS ET REGIENSIS
1175
UNIMORE
UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

CLINICA MALATTIE APPARATO RESPIRATORIO MODENA

Le nuove terapie nella BPCO

Enrico Clini

Outline

- Combination treatments for COPD
- Treatable traits in COPD
- New drugs for COPD

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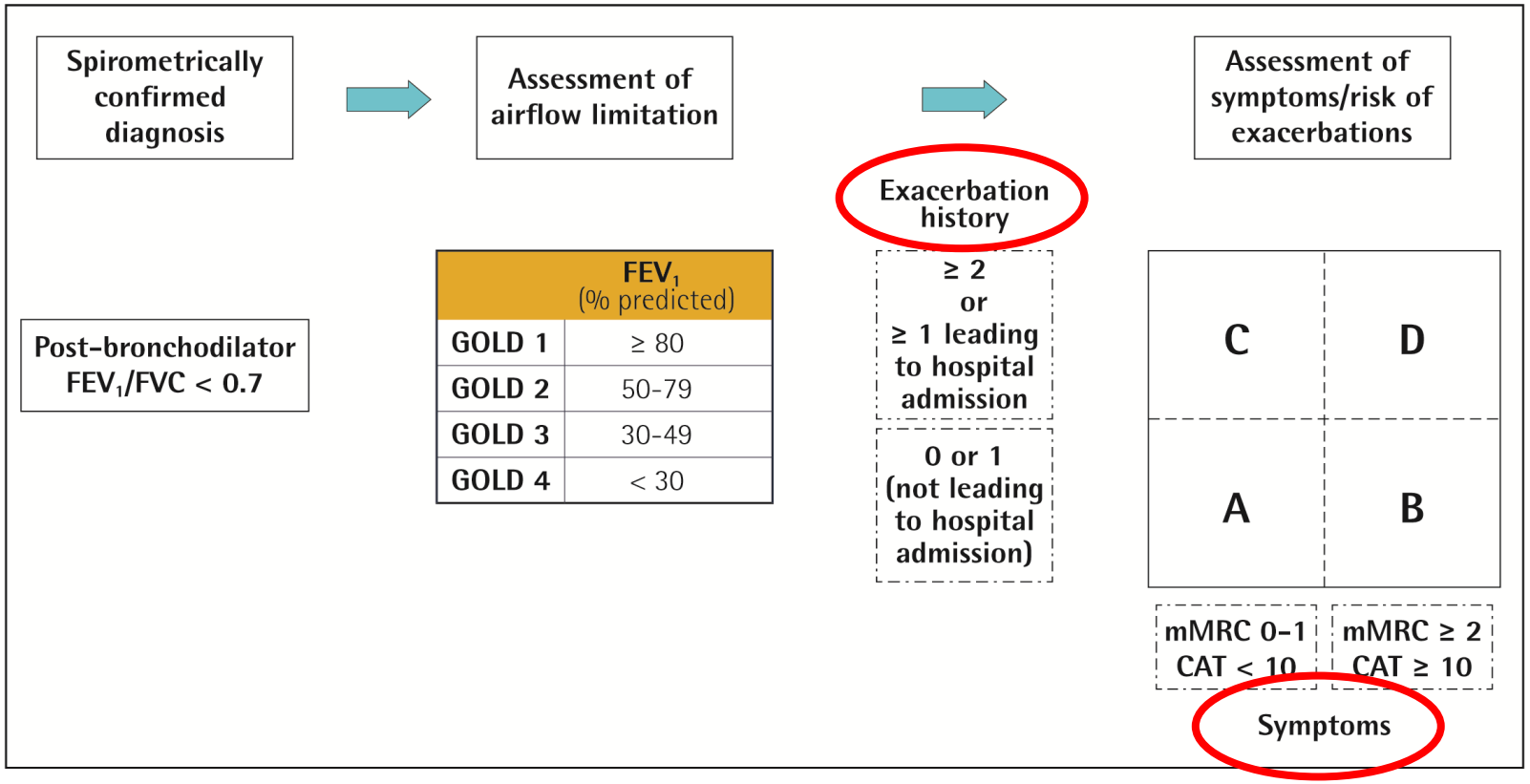
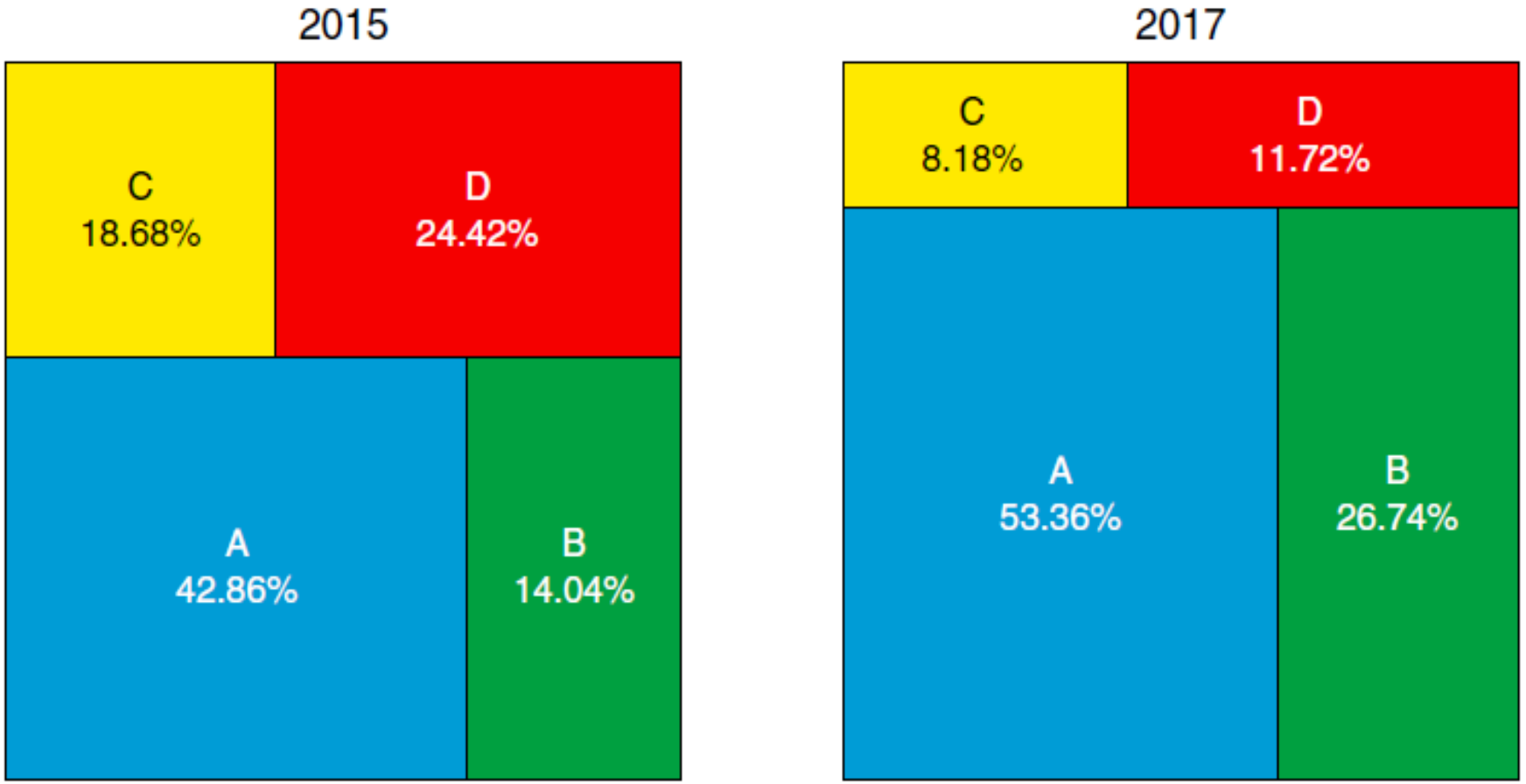
- Combination treatments for COPD
- Treatable traits in COPD
- New drugs for COPD

Assessment Tool in COPD





Cabrera López C, et al. AJRCCM 2018

Treatment goals in COPD

REDUCE

Perceived symptoms

PREVENT

Future risk of AE

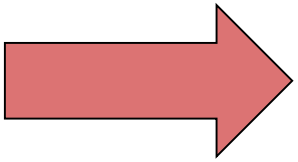
Active inhaled drugs in COPD

- **Anti-muscarinic bronchodilators (LAMA)**
- **Beta-agonists bronchodilators (LABA)**
- **Steroids (ICS)**

Treatment of COPD

If increasing

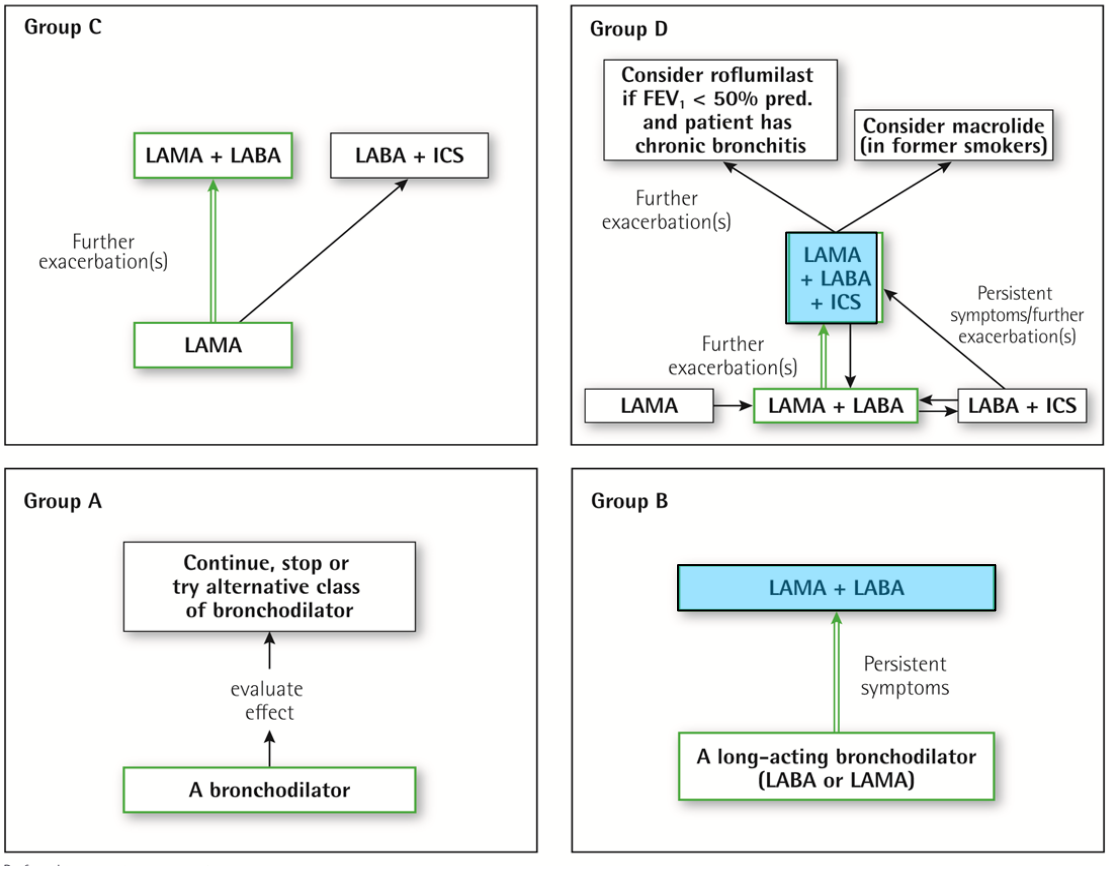
Symptoms
and/or
Risk of AE



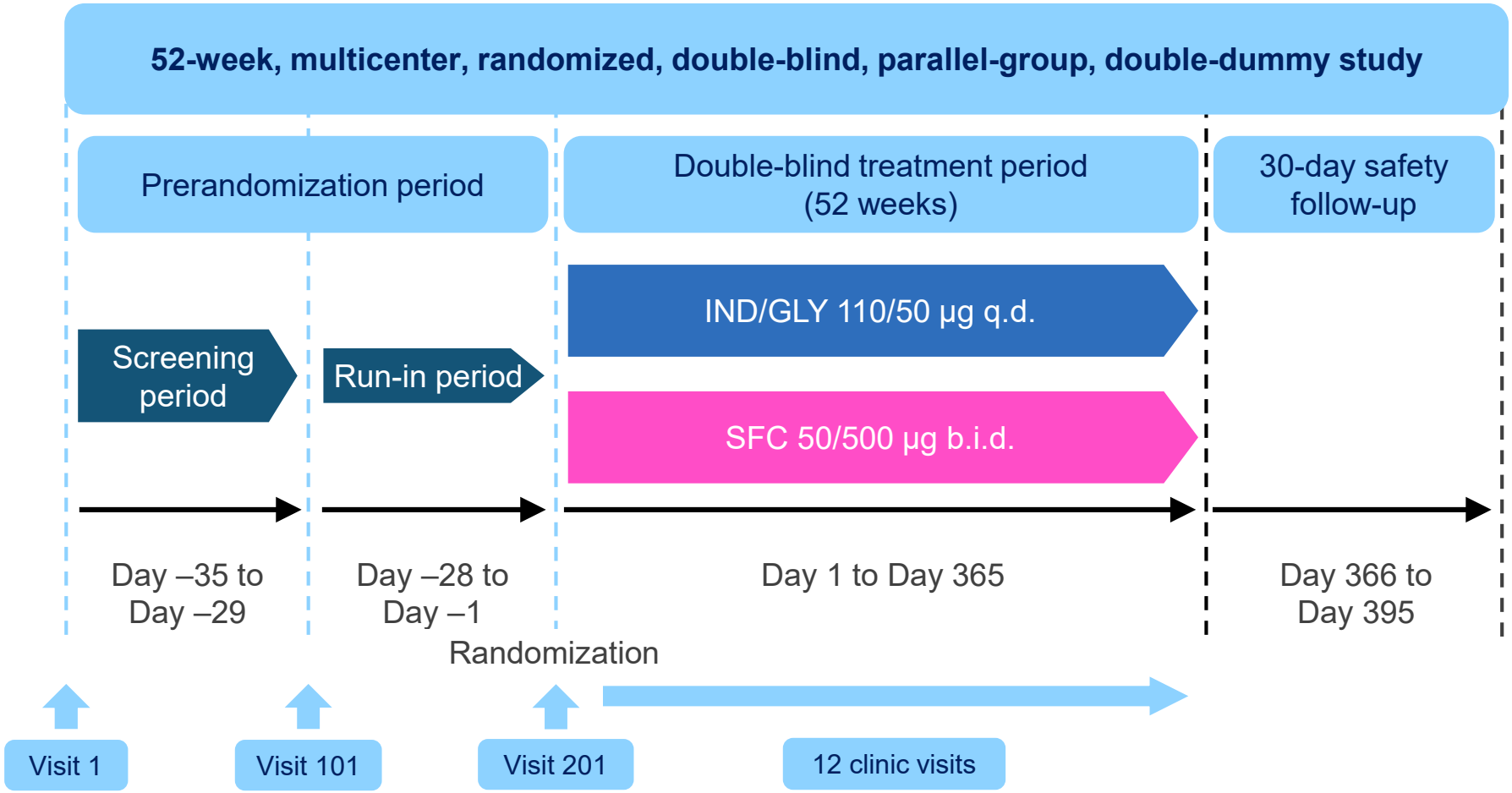
Then increasing

Medications

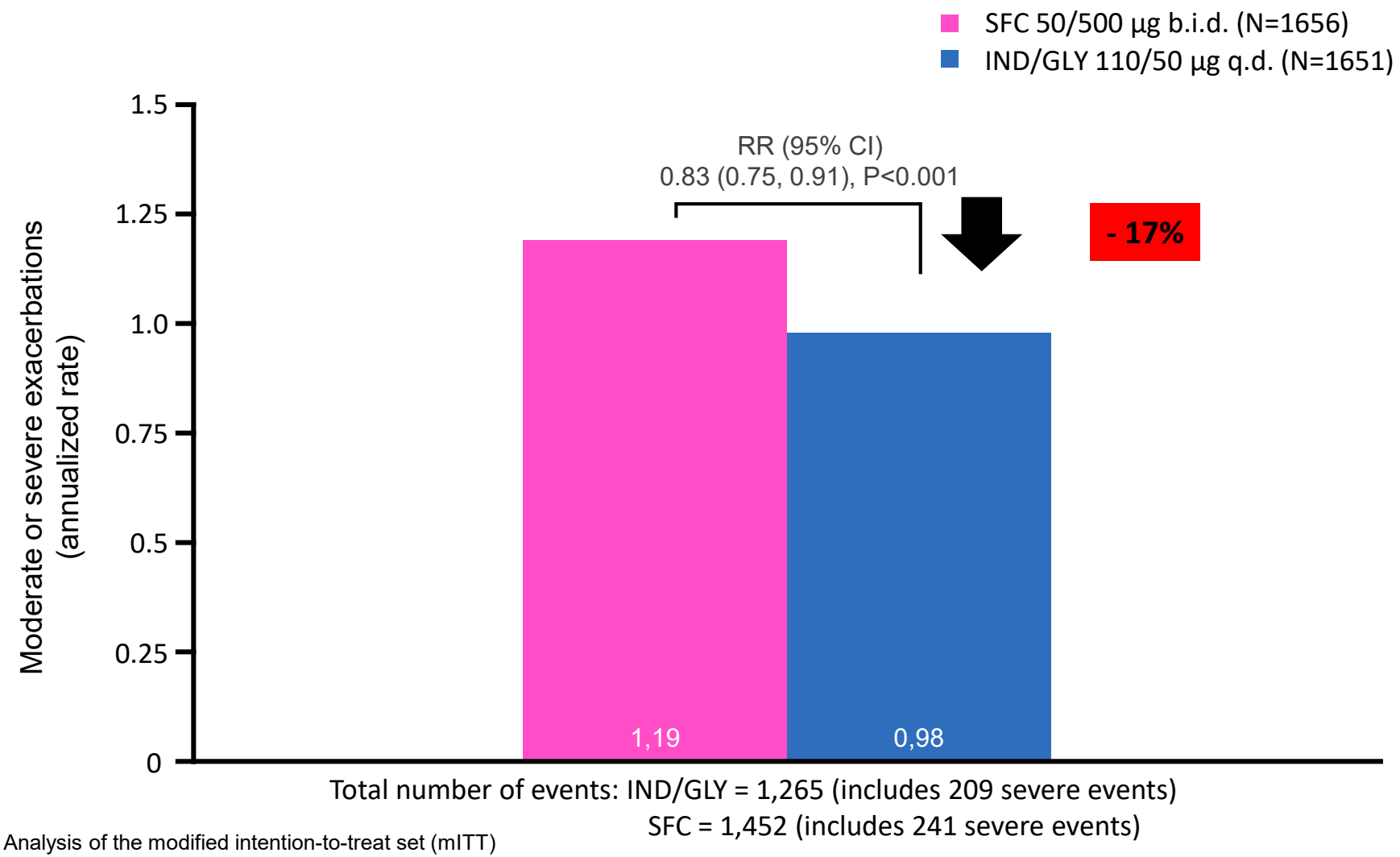
Treatment algorithm in COPD



The FLAME trial



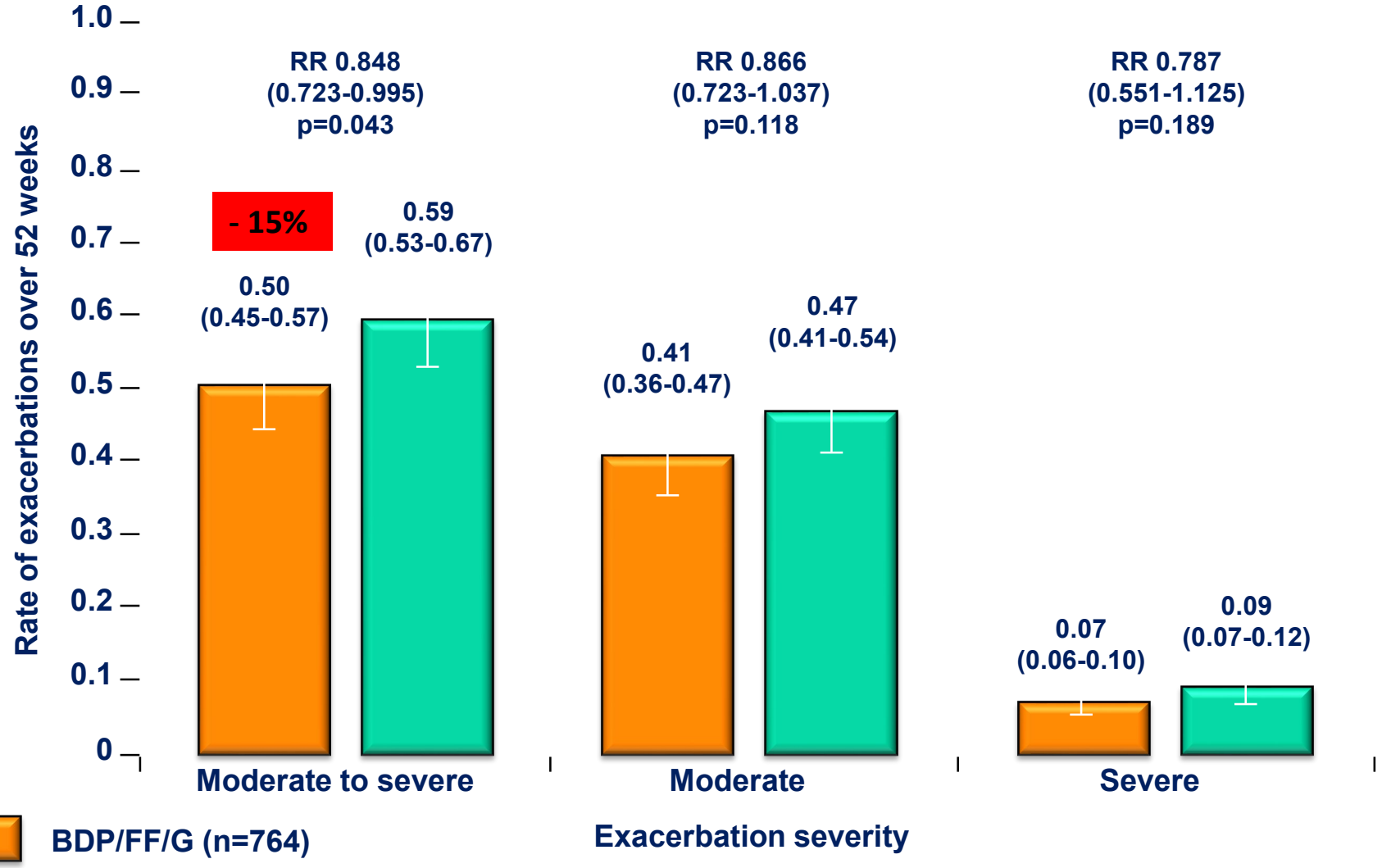
Wedzicha JA, et al. NEJM 2016



Analysis of the modified intention-to-treat set (mITT)

Wedzicha JA, et al. NEJM 2016

The TRIBUTE trial



Papi A, et al. Lancet 2018

Global risk reduction with TRIPLE

Number (%) of patients	BDP/FF/G (N=764)	IND/GLY (N=768)
Adverse events	490 (64.1)	516 (67.2)
COPD worsening	273 (35.7)	288 (37.5)
Pneumonia	28 (3.7)	27 (3.5)
Cough	13 (1.7)	25 (3.3)
Hypertension	15 (2.0)	26 (3.4)
Ischemic heart disease	8 (1.0)	16 (2.1)
Serious adverse events	117 (15.3)	130 (16.9)
COPD worsening	61 (8.0)	69 (9.0)
Death	3 (0.4)	8 (1.0)
Ischemic heart disease	2 (0.3)	11 (1.4)
Myocardial infarction	1 (0.1)	8 (1.0)
Atrial fibrillation	0	7 (0.9)

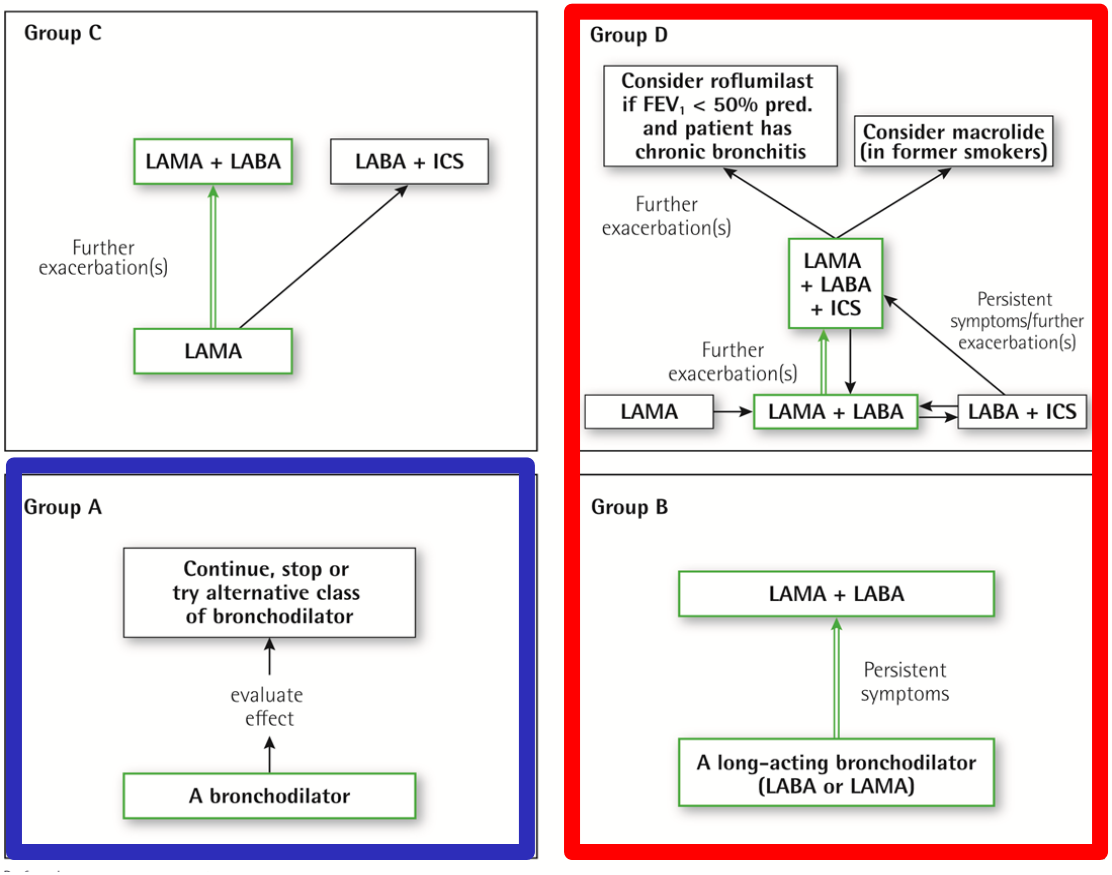
Papi A, et al. Lancet 2018

Global risk reduction with TRIPLE
(pooled data from Trilogy-Trinity-Tribute)

	BDP/FF/G, BDP/FF, BDP/FF+TIO (n=3745)	TIO, IND/GLY (N=1844)	
	N of patients with events (%)		HR (95%, CI), p-value
RESPIRATORY	19 (0.5%)	9 (0.5%)	1.01 (0.45; 2.22) p=0.990
NON-RESPIRATORY	56 (1.5%)	41 (2.2%)	0.65 (0.43; 0.97) p=0.037

Scuri M, et al. AJRCCM 2018 (abstract)

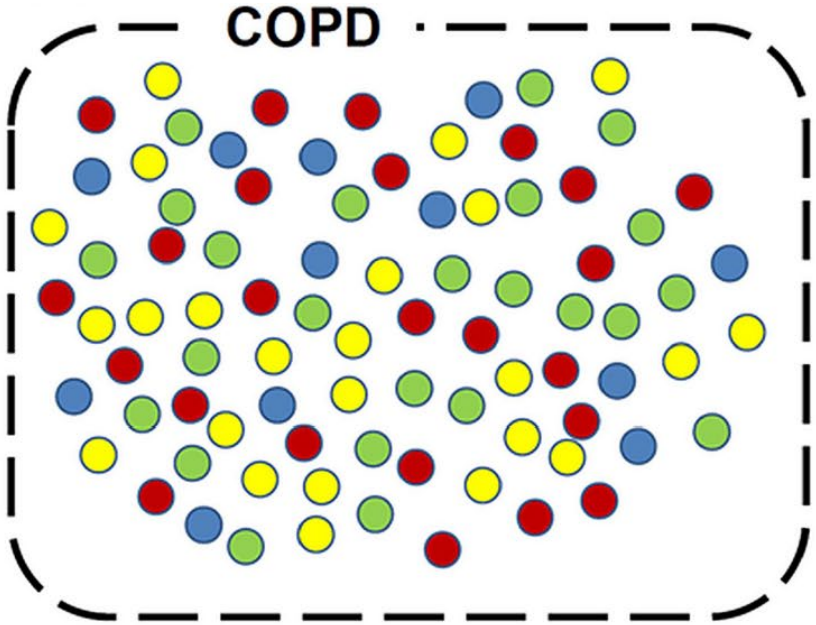
Treatment algorithm in COPD

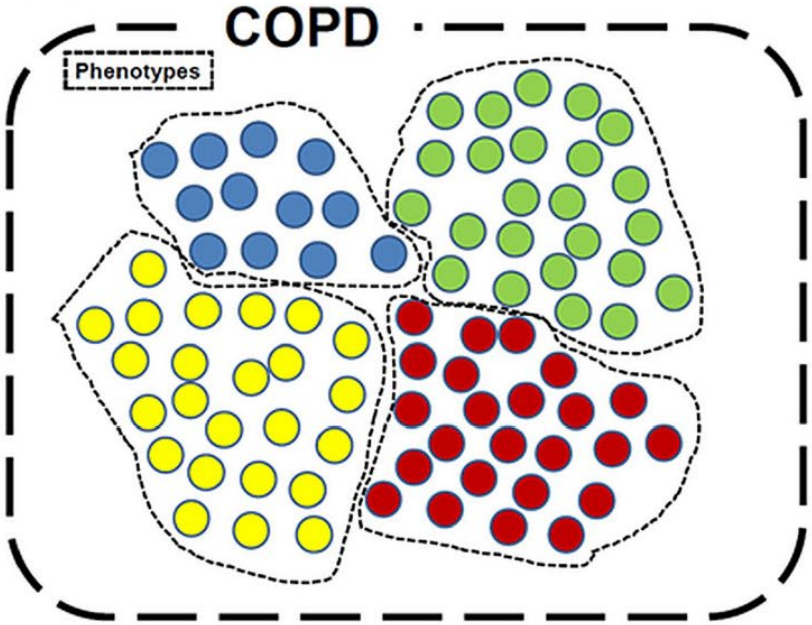


Outline

- Combination treatments for COPD
- Treatable traits in COPD
- New drugs for COPD

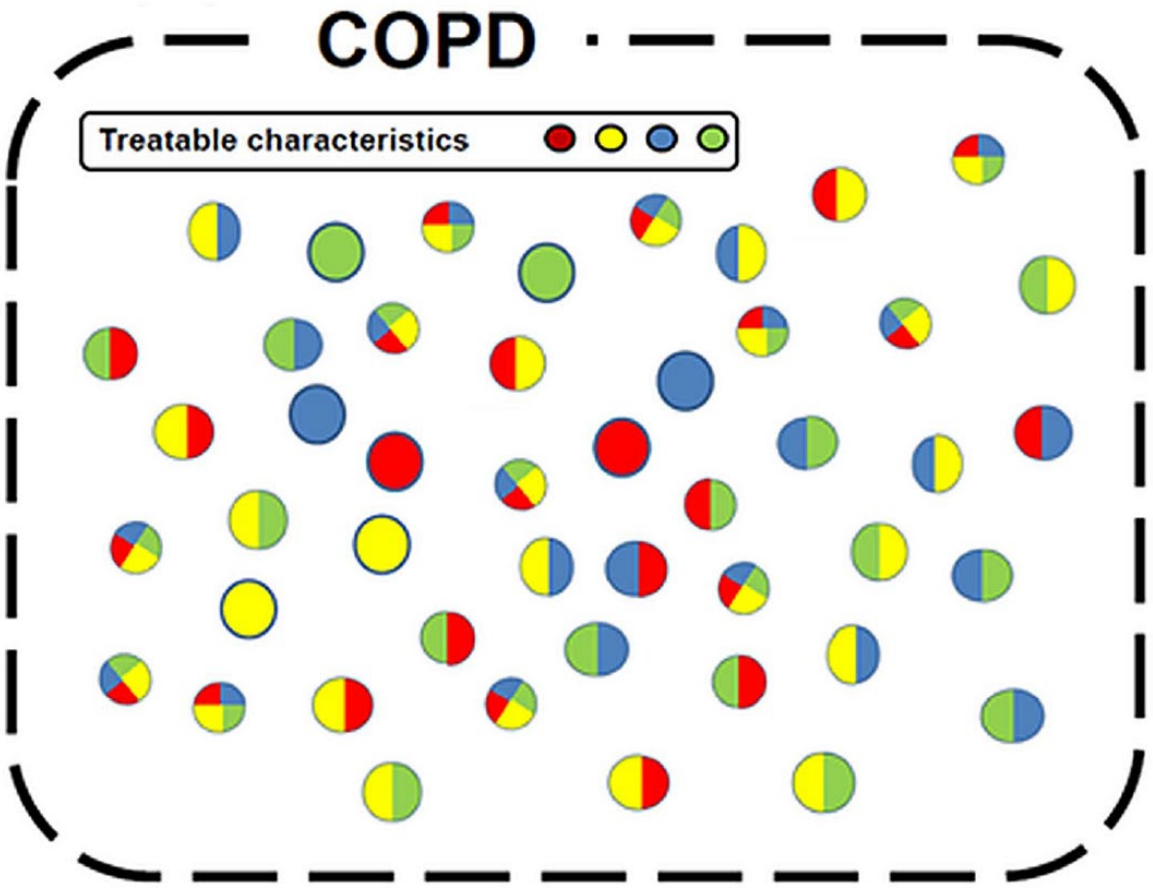
The path to personalised medicine in COPD





Agusti A. Thorax 2014

The path to personalised medicine in COPD



Agusti A. Thorax 2014

Pulmonary treatable traits of airway diseases

Treatable traits (can coexist)	Imp.	Rec.	Diagnostic criteria	Treatment			Main expected benefit
				First choice	Efficacy	Second choice	
Airflow limitation [9]	+++	+++	FEV_1/FVC <0.7 (or lower limit of normal)				S
Airway smooth muscle contraction	++	+++	Bronchodilator reversibility, peak expiratory flow variability, positive PC_{20}	Maintenance: long-acting β_2-adrenergic agonists/muscarinic antagonists; rescue: short-acting β_2-adrenergic agonists/muscarinic antagonists	+++	Inhaled corticosteroids, *bronchial thermoplasty*¶	S
Loss of elastic recoil (emphysema)	+++	++	Chest computed tomography, D_{LCO}, compliance	Smoking cessation	+	Lung volume reduction surgery, lung transplantation, α_1-anti-trypsin replacement if deficient, *valves*, *coils*	S, P
Airway mucosal oedema	++	+	*Chest computed tomography, spirometry-induced bronchoconstriction*	Inhaled corticosteroids	++	Oral corticosteroids, *anti-interleukin-5, -13, -4*	E
Eosinophilic airway inflammation [55, 56]	+++	+++	Sputum eosinophils, blood eosinophils, F_{ENO}, (*periostin*)	Inhaled corticosteroids	+++	Oral corticosteroids, leukotriene receptor antagonists, anti-IgE, *anti-interleukin-5, -13, -4*	E
Chronic bronchitis	++	+++	Cough and sputum 3 months×2 years (no eosinophilic airway inflammation)	Smoking cessation	+	Carbocysteine, macrolides, roflumilast	E
Airway bacterial colonisation #	++	++	Sputum culture, *quantitative PCR*	Antibiotics	++	*Long-term low-dose macrolides, vaccination*	E/S
Bronchiectasis #	++	++	Chest computed tomography	Drainage	+	Macrolides, nebulised antibiotics, surgery, vaccination	E/S
Cough reflex hypersensitivity [49, 57]	++	+++	Capsaicin challenge, cough counts, cough questionnaire	Speech and language treatment [58]	+	*Gabapentin* [56]	S
Pre-capillary pulmonary hypertension #	++	++	Doppler echocardiography, brain natriuretic peptide, right heart catheterisation	Long-term (domiciliary) oxygen therapy	++	Noninvasive ventilation, lung transplantation	S, E, P
Chronic respiratory failure #							
Arterial hypoxaemia	+++	+++	P_{aO_2} <55 mmHg	Long-term (domiciliary) oxygen therapy	++		P
Arterial hypercapnia	+++	+++	P_{aCO_2} >45 mmHg		+	Noninvasive ventilation, lung transplantation	

Agusti A, et al. ERJ 2016

EXPERT OPINION ON PHARMACOTHERAPY, 2016
VOL. 17, NO. 7, 977–988
http://dx.doi.org/10.1517/14656566.2016.1155555

Taylor & Francis
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REVIEW

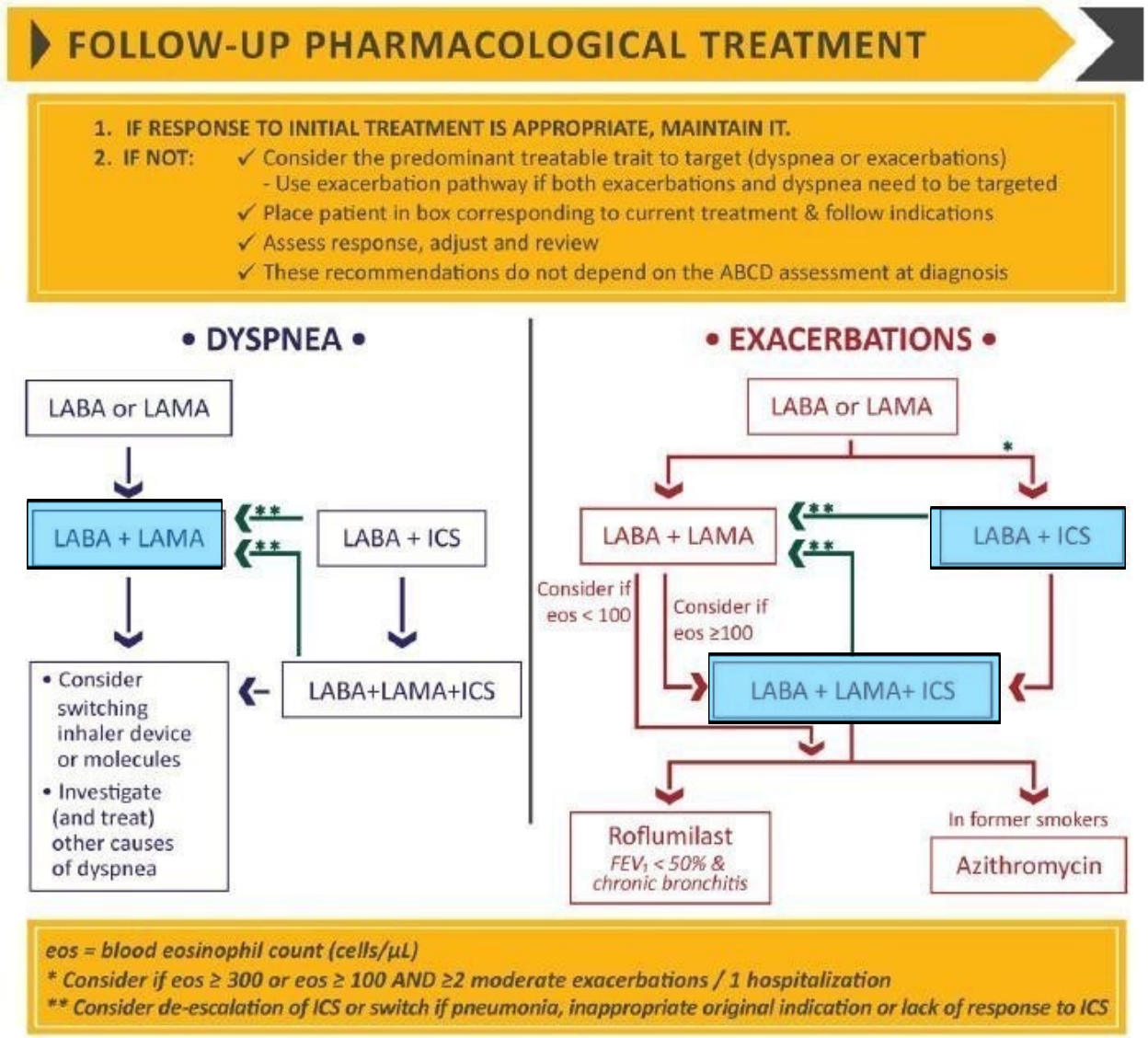
Treatment options for moderate-to-very severe chronic obstructive pulmonary disease

Mario Cazzola[a], Paola Rogliani[a], Josuel Ora[a] and Maria Gabriella Matera[b]

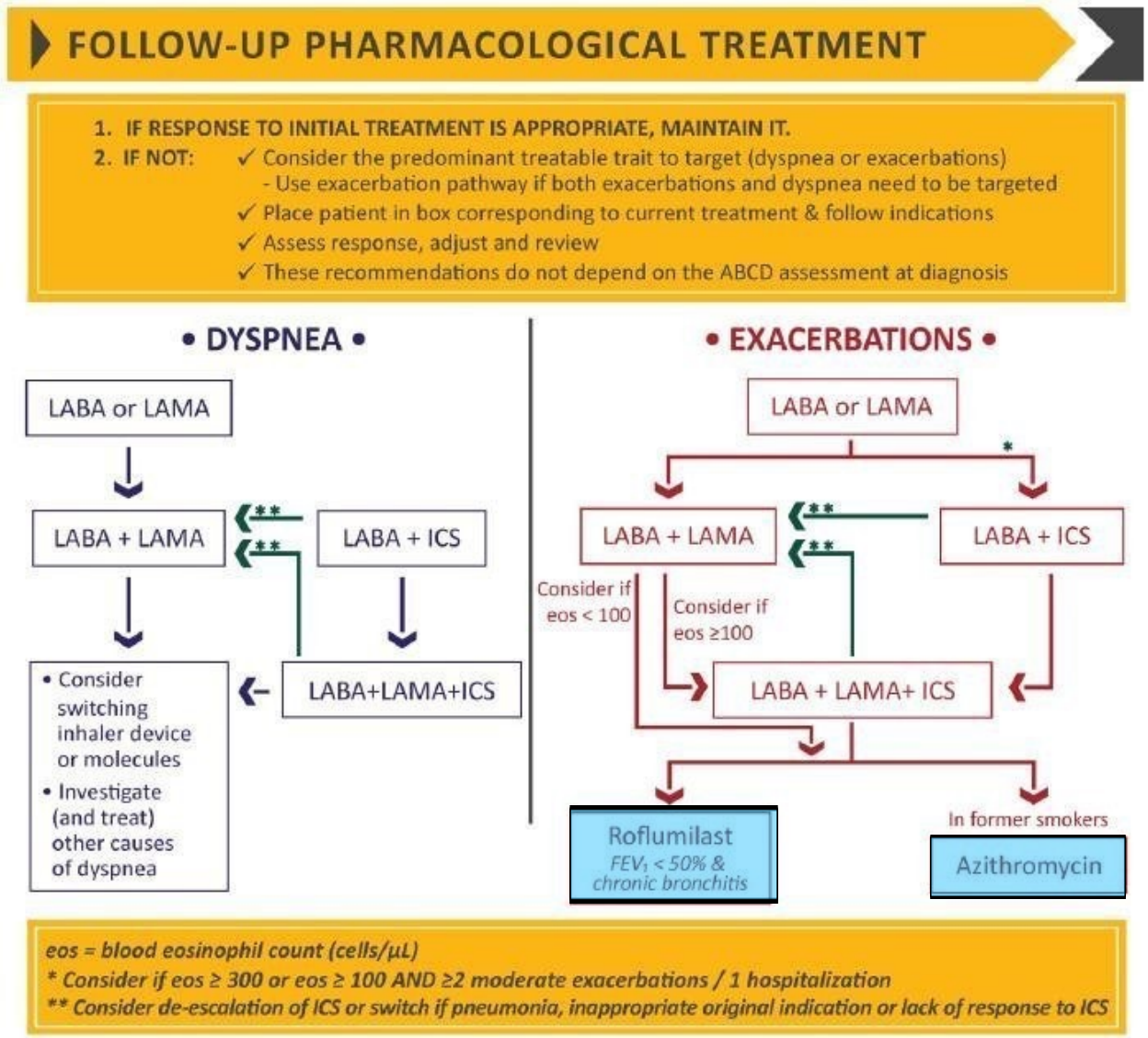
PULMONARY

- **Eosinophilic inflammation**
- **PDE4 inhibitors**
- **Antibiotics as immunomodulant agents**
- **Mucolytic agents**
- **Immunostimulation with bacterial lysates**
- **Alpha-1-antitrypsin augmentation therapy**

Moving forward – GOLD 2018



Moving forward – GOLD 2018



Luo *et al. Respiratory Research* (2016) 17:18
DOI 10.1186/s12931-016-0330-y

Respiratory Research

RESEARCH Open Access

Can roflumilast, a phosphodiesterase-4 inhibitor, improve clinical outcomes in patients with moderate-to-severe chronic obstructive pulmonary disease? A meta-analysis

Jian Luo[1†], Ke Wang[1†], Dan Liu[2], Bin-Miao Liang[1,3*†] and Chun-Tao Liu[1,3*†]

Roflumilast can be considered as an adjunctive therapy in selective patients with moderate-to-severe COPD with frequent AE due to the effect of lung function improvement, dyspnea alleviation and acute exacerbation decrease

PLOS | ONE

RESEARCH ARTICLE

Prophylactic Use of Macrolide Antibiotics for the Prevention of Chronic Obstructive Pulmonary Disease Exacerbation: A Meta-Analysis

Wentao Ni[1☯], Xiaodi Shao[1☯], Xuejiu Cai[1], Chuanqi Wei[1], Junchang Cui[1]*, Rui Wang[2], Youning Liu[1]

PLOS ONE | DOI:10.1371/journal.pone.0121257 March 26, 2015

6-12 months erythromycin or azithromycin therapy could effectively reduce the frequency of exacerbations in selected patients with COPD and high risk of AE.

However, long-term treatment may bring increased adverse events and the emergence of macrolide-resistance.

EXPERT OPINION ON PHARMACOTHERAPY, 2016
VOL. 17, NO. 7, 977–988
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- **Antibiotics as immunomodulant agents**
- **Mucolytic agents**
- **Immunostimulation with bacterial lysates**
- **Alpha-1-antitrypsin augmentation therapy**

Extra-pulmonary treatable traits of airway diseases

Treatable traits (can coexist)	Imp.	Rec.	Diagnostic criteria	Treatment			Main expected benefit
				First choice	Efficacy	Second choice	
Deconditioning	+	+	Cardio-pulmonary exercise testing, 6-min walking distance	Exercise, rehabilitation	+		S, P
Obesity	+	+++	Body mass index	Diet, physical activity	+	Medication, bariatric surgery	S, P
Cachexia	+	+++	Body mass index	Diet, physical activity	+		S, E
Obstructive sleep apnoea syndrome	+	++	Questionnaires, polysomnography	Continuous positive airway pressure	+	Weight loss, mandibular advancement splint	S, P
Cardiovascular disease	++	+++	Electrocardiogram, Doppler echocardiography, brain natriuretic peptide	Angiotensin-converting enzyme inhibitors, diuretics, β-blockers	++	Surgery	S, E, P
Gastro-oesophageal reflux disease [59]	+	++	Gastrointestinal endoscopy, pH monitoring	Proton pump inhibitors, H_2 antagonist	+	Surgery	S
Upper airway diseases: rhino-sinusitis	+	++	History and examination, imaging	Topical steroids	++	Leukotriene receptor antagonists, antihistamines, surgery	S, E
Upper airway diseases: inducible laryngeal obstruction (vocal cord dysfunction)	++	+	Fibre optic laryngoscopy, flow-volume curve, dynamic neck computed tomography	Speech pathology therapy [58]	++	*Laryngeal botulinum toxin, psychology/ psychiatry*	S
Psychiatric disorders: depression	++	++	Questionnaires, psychologist/liaison psychiatrist assessment	Cognitive behavioural therapy, pharmacotherapy	++		S
Psychiatric disorders: anxiety/other behavioural aspects including breathing pattern disorders	++	++	Questionnaires, psychologist/liaison psychiatrist assessment	Anxiety management, breathing retraining	+	*Anxiolytic/ antidepressant medication, cognitive behavioural therapy, psychotherapy*	S
Persistent systemic inflammation [60, 61]	++	++	High-sensitivity C-reactive protein		?	*Statins*	S, E, P

Agusti A, et al. ERJ 2016

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EXTRA-PULMONARY

- **Integrating management of COPD comorbidities**
  - **Statins**
  - **ACE inhibitors and AT1-receptor blockers**
  - **β-blockers**
  - **Antiplatelet agents**

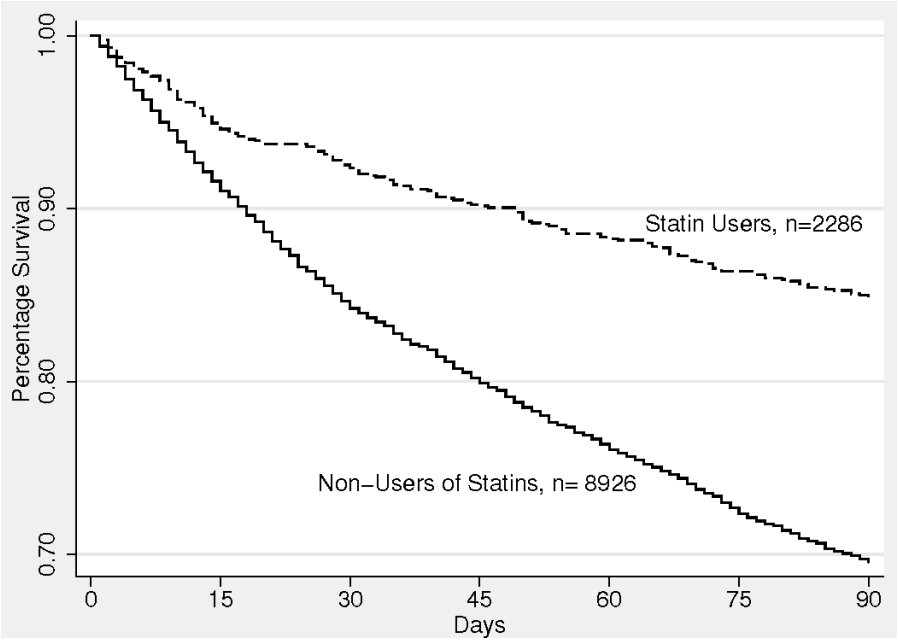
Research

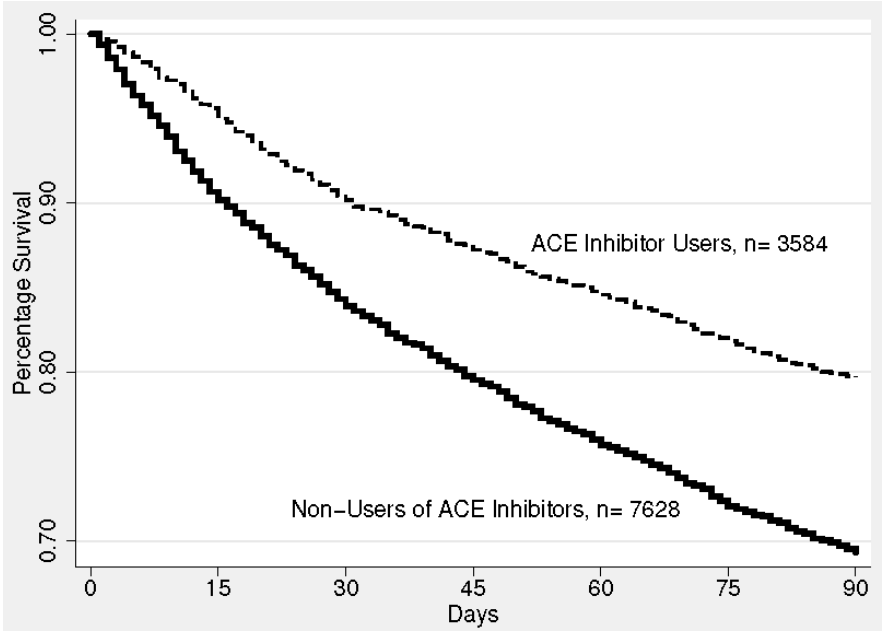
Open Access

Impact of statins and ACE inhibitors on mortality after COPD exacerbations

Eric M Mortensen*[1,2], Laurel A Copeland[1,3], Mary Jo V Pugh[1,4], Marcos I Restrepo[1,5], Rosa Malo de Molina[1,5], Brandy Nakashima[1] and Antonio Anzueto[1,5]

Respiratory Research 2009, 10:45





Use of statins and/or ACE inhibitors prior to admission is associated with lower mortality risk in subjects hospitalized with AECOPD

	IRR	95% CI		p Value
A (n=719)				
Total	2.02	1.20	3.38	0.008
Severe	0.91	0.31	2.65	0.862
B (n=856)				
Total	0.45	0.28	0.74	0.002
Severe	0.27	0.09	0.76	0.014
C (n=201)				
Total	1.27	0.49	3.26	0.626
Severe	0.50	0.04	6.06	0.590
D (n=1688)				
Total	0.68	0.51	0.92	0.011
Severe	0.71	0.47	1.06	0.097

Total exacerbation rates adjusted for age, gender, FEV_1, %emphysema on CT, coronary artery calcification, presence of CAD, long-acting respiratory medications and for the propensity to prescribe β-blockers based on demographics, CAD, congestive heart failure and severity of airflow obstruction.
Severe exacerbation rates adjusted for age, race, FEV1, %emphysema on CT, coronary artery calcification, presence of congestive heart failure, long-acting respiratory medication, and for the propensity to prescribe β-blockers. All values expressed as IRRs (95% CIs).
GOLD, Global Initiative for Chronic Obstructive Lung Disease.

β-blockers are associated with a significant reduction in AECOPD risk across ABCD-categories

Bhatt SP, et al. (COPDGene Investigators) Thorax 2016

COPD: JOURNAL OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE
2015, VOL. 0, NO. 0, 1–5
http://dx.doi.org/10.3109/15412555.2015.1099620

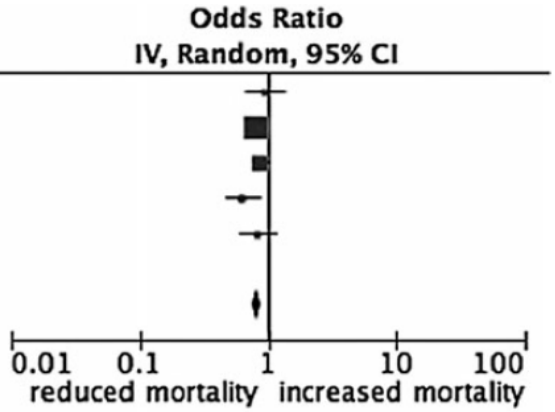
Taylor & Francis
Taylor & Francis Group

Antiplatelet Treatment Reduces All-Cause Mortality in COPD Patients: A Systematic Review and Meta-Analysis

Rita Pavasini[a], Simone Biscaglia[a], Fabrizio d'Ascenzo[b], Annamaria Del Franco[a], Marco Contoli[c], Fatima Zaraket[a], Federico Guerra[e], Roberto Ferrari[a,d,f], and Gianluca Campo[a,d]

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
soyseth 2007	−0.06	0.17	5.6%	0.94 [0.67, 1.31]	2007
short 2011	−0.22	0.05	51.3%	0.80 [0.73, 0.89]	2011
ekstrom 2012	−0.15	0.07	29.5%	0.86 [0.75, 0.99]	2012
harrison 2014	−0.46	0.15	7.2%	0.63 [0.47, 0.85]	2014
campo 2015	−0.19	0.16	6.3%	0.83 [0.60, 1.13]	2015
Total (95% CI)			**100.0%**	**0.81 [0.75, 0.88]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.33$, $df = 4$ ($P = 0.36$); $I^2 = 8\%$
Test for overall effect: $Z = 5.03$ ($P < 0.00001$)

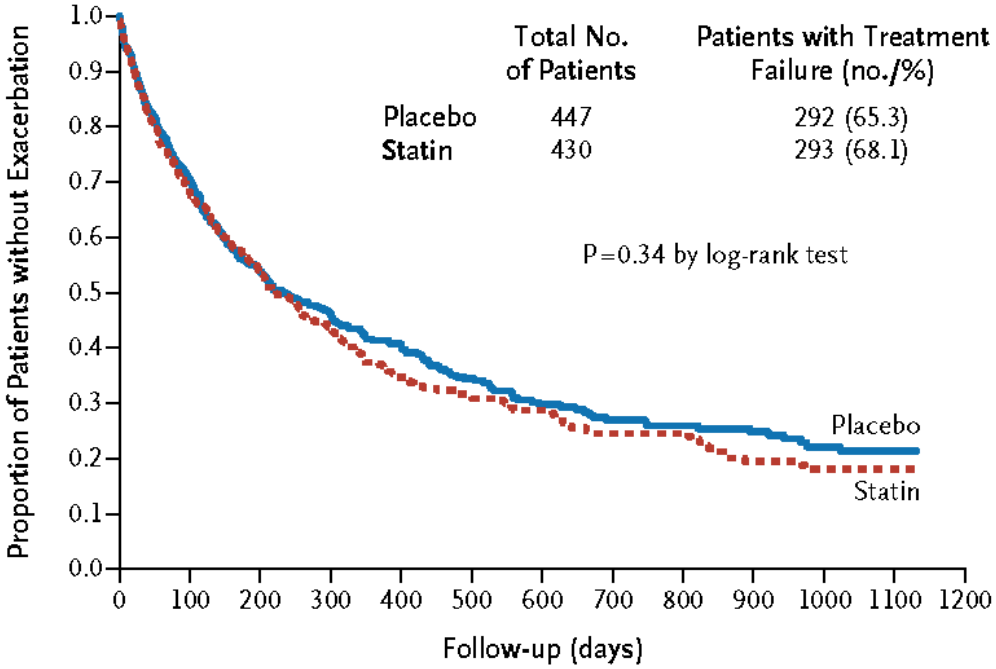


Anti-PTL therapy contribute to reduce the risk of all-cause mortality in COPD patients

Simvastatin for the Prevention of Exacerbations in Moderate-to-Severe COPD

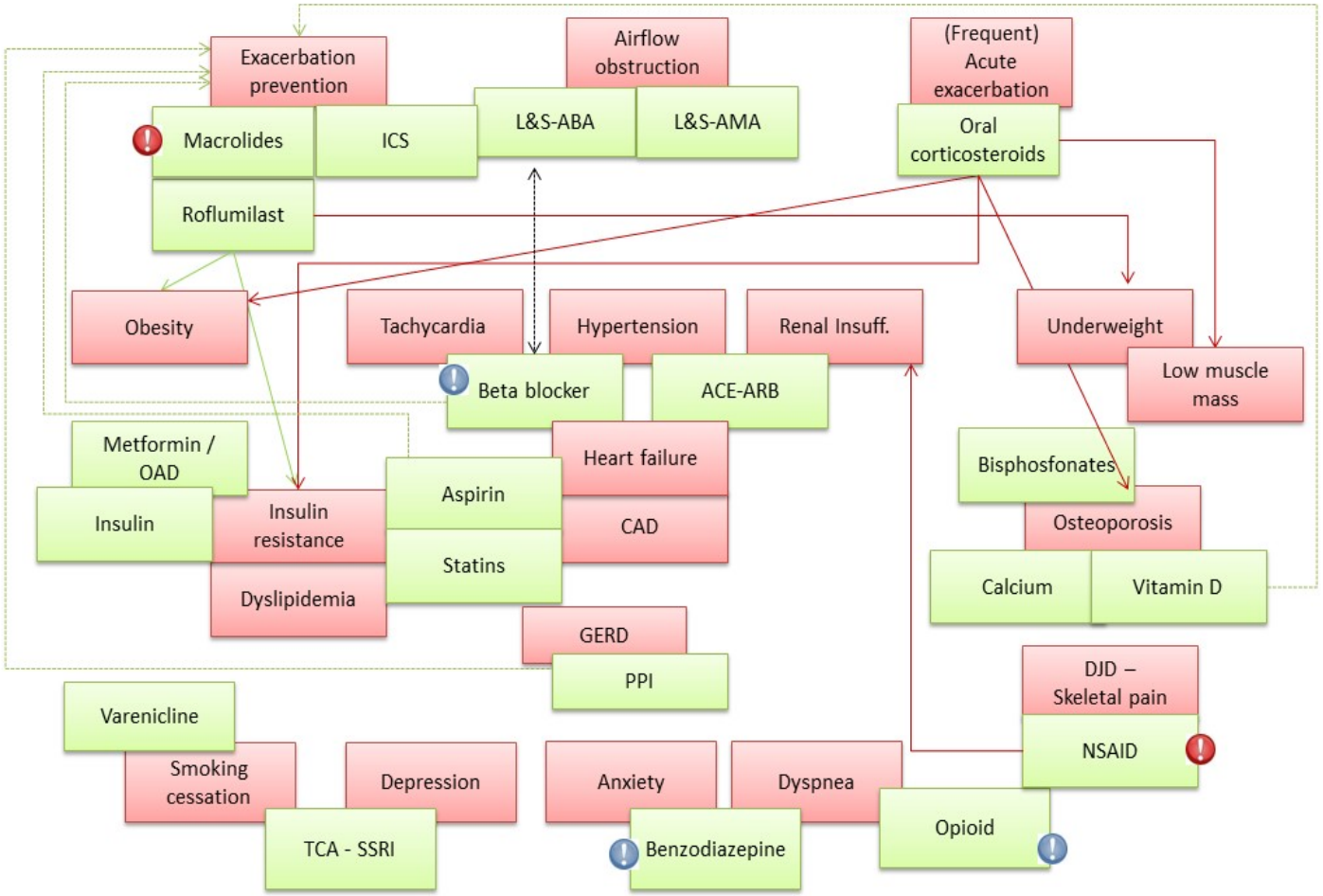
G.J. Criner, J.E. Connett, S.D. Aaron, R.K. Albert, W.C. Bailey, R. Casaburi, J.A.D. Cooper, Jr., J.L. Curtis, M.T. Dransfield, M.K. Han, B. Make, N. Marchetti, F.J. Martinez, D.E. Niewoehner, P.D. Scanlon, F.C. Sciurba, S.M. Scharf, D.D. Sin, H. Voelker, G.R. Washko, P.G. Woodruff, and S.C. Lazarus, for the COPD Clinical Research Network and the Canadian Institutes of Health Research

N Engl J Med 2014;370:2201-10.



In the STATCOPE trial, there were no significant between-group differences in the time to the first AE

DRUG MANAGEMENT OF COMPLEX COPD WITH COMORBIDITIES



Vanfleteren L, et al. Lancet Respir Med 2016

Outline

- Combination treatments for COPD
- Treatable traits in COPD
- New drugs for COPD

NEW CATEGORIES OF (potentially) EFFECTIVE DRUGS

- Monoclonal Antibodies
- Bifunctional (sinergistic) drugs
- Inhaled BNP

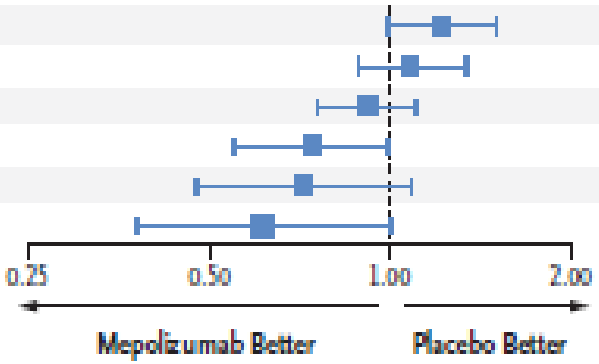
Monoclonal Antibodies

Biological target	Biological agent	Impact in COPD
TNFα	Etanercept	Reduction in the rate of COPD hospitalization (evidence from a retrospective, observational, non-randomized, administrative database study)
		Not more effective than prednisone for the treatment of acute exacerbations of COPD (evidence from a proof-of-concept RCT)
	Infliximab	No beneficial effects on various clinical parameters (evidence from a phase II RCT)
IL-1	Canakinumab	Ineffective in the treatment of stable COPD (evidence from a phase I/II RCT)
	MEDI8986	No effect in moderate-to-very-severe COPD (evidence from a phase II RCT)
IL-4	NA	Not tested
IL-5	Mepolizumab	No improvement in lung function and exacerbation rates after 6-months of treatment in patients with current moderate-to-severe COPD with sputum eosinophilia. Clinically meaningful (>0.5 units) improvement of CRQ mean dyspnoea domain score (evidence from a phase III RCT)
		Ongoing phase III RCTs
	Benralizumab	No influence on the rate of acute exacerbations of COPD in patients with moderate-to-severe COPD, having had at least one acute exacerbation of COPD, and a sputum eosinophil count ≥3 % within the previous year. Reduction of COPD exacerbations and improved lung function, as well as disease-specific health status in patients with higher baseline levels of blood eosinophils (>200 cells/μl) [evidence from a phase II RCT]
		Ongoing phase III RCTs
IL-6	NA	Not tested
CXCL8 (IL-8)	ABX-CXCL8	Improved the transition dyspnoea index (evidence from a pilot RCT)
IL-13	Lebrikizumab	Ongoing phase II RCT
IL-17	CNTO6785	Completed phase II RCT, no results available
IL-23	NA	Not tested
IL-33	AMG 282	Headed into phase II RCT
TGF-β	NA	Not tested

Matera MG, et al. Drugs 2016

Mepolizumab – AECOPD risk reduction

Blood Eosinophil Count	Mepolizumab Group	Placebo Group	Rate Ratio (95% CI)
cells/mm³	*no. of patients with event/total no. of patients*		
<150 with no historical count ≥300	184/184	190/190	1.23 (0.99–1.51)
<150 regardless of historical count	236/640	230/645	1.10 (0.91–1.34)
≥150 to <300	237/456	235/455	0.92 (0.76–1.11)
≥300 to <500	112/456	110/455	0.75 (0.55–1.00)
≥500	53/456	67/455	0.72 (0.48–1.09)
<150 with historical count ≥300	53/456	42/455	0.64 (0.40–1.03)



Effect of 100-mg MEPO versus placebo (meta-analysis of data from the METREX and METREO trial based on modified ITT populations)

Pavord I, et al. NEJM 2017

Bifunctional Drugs

Class/agent	Stage of development	Pros	Cons
MABAs		Enhanced patent position A single molecule that confers both therapeutic effects can avoid the approval of each component separately as well as in combination, and may be a faster and less expensive route to regulatory approval They offer the benefit of delivering a fixed ratio into every region of the lung reducing the complexity of combination inhalers, a single pharmacokinetic profile, a uniform ratio of activities at the cellular level and a simplified clinical development programme As MABAs offer benefits in terms of ease-of-use, convenience and, consequently, compliance, adherence to the prescribed treatment, would probably be improved Patients cannot take one agent without taking the other	The ratio of muscarinic antagonism and β_2-agonism activities cannot be adjusted as needed and this limits dosing flexibility The combination of muscarinic antagonism and β_2-agonism activities might theoretically cause a downregulation of β_2-adrenoceptors and an upregulation of muscarinic acetylcholine receptors Not clear whether the drug should be dosed for the β_2 agonist activity or the muscarinic receptor antagonist activity
GSK961081	Phase III		
AZD2115	Phase II		
LAS190792	Phase I		
THRX200495	Preclinical		
TEI3252	Preclinical		
PF3429281	Discontinued		
PF4348235	Discontinued		
Inhaled nitric oxide-donating analogues		Improved anti-inflammatory effects compared to budesonide (TPI 1020) Improved bronchodilator effects compared to salbutamol due to the release of NO (NCX 950)	Limited clinical efficacy
TPI 1020	Discontinued		
NCX 950	Discontinued		
PDE3/4 inhibitors		The combination of both bronchodilator (PDE3 mediated) and anti-inflammatory activity (PDE3 and PDE4 mediated) could result in an enhanced overall efficacy profile compared with selective PDE4 inhibitors PDE3 (which is predominantly localised to the particulate cellular fraction) and PDE4 (which is predominantly cytosolic) can regulate different pools of cAMP	There are concerns about the potential cardiovascular toxicity of PDE3 inhibition Further studies are needed to better understand the full potential of this novel therapy for COPD and asthma
RPL554	Phase II		
KCA-1490	Preclinical		
Other bifunctional PDE inhibitors		The combination of both anti-inflammatory (PDE4 mediated) and bronchodilator (mediated by β_2-agonism or M3-receptor antagonism) activity could result in an enhanced overall efficacy profile compared with selective PDE4 inhibitors	There are very limited biological data
Dual PDE4 inhibitor/β_2-agonist			
GS-5759	Preclinical		
Hybrids that combine both salmeterol and the PDE4 inhibitors roflumilast or phthalazinone	Preclinical		
Dual PDE4 inhibitor/ M3-receptor antagonist			
UCB-101333-3	Discontinued		
IL-4/IL-13 dual antagonists		Reduce the IL-4-dependent rise in serum IgE, and reduce IL-13-dependent BHR, lung inflammation, mucin gene expression and serum chitinase responses in mice Might provide robust efficacy in the treatment of asthma and other Th2-driven diseases	Different studies and different agents can produce different effects
Dupilumab	Phase II		
AMG 317	Phase II		
Pitrakinra	Phase II		

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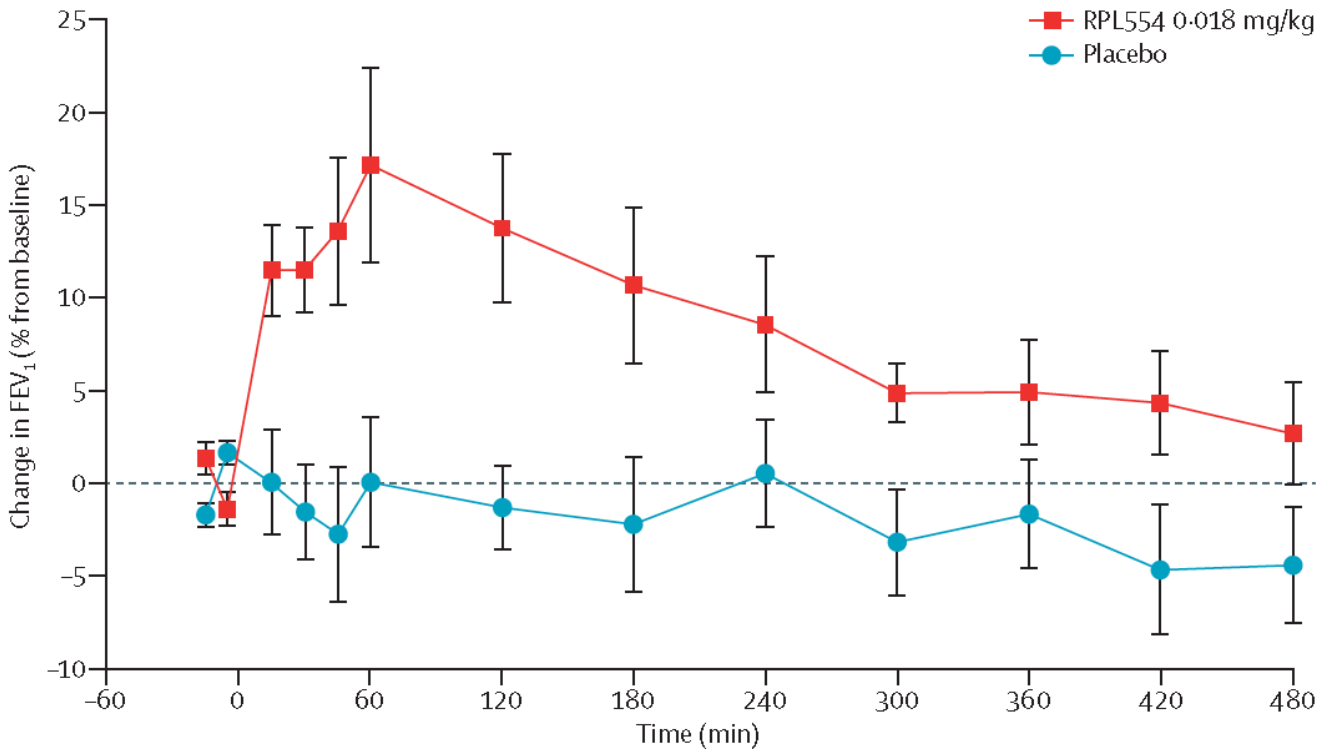
Efficacy and safety of RPL554, a dual PDE3 and PDE4 inhibitor, in healthy volunteers and in patients with asthma or chronic obstructive pulmonary disease: findings from four clinical trials

Lui G Franciosi, Zuzana Diamant, Katharine H Banner, Rob Zuiker, Nicoletta Morelli, Ingrid M C Kamerling, Marieke L de Kam, Jacobus Burggraaf, Adam F Cohen, Mario Cazzola, Luigino Calzetta, Dave Singh, Domenico Spina, Michael J A Walker, Clive P Page

Lancet Respir Med 2013; 1: 714–27

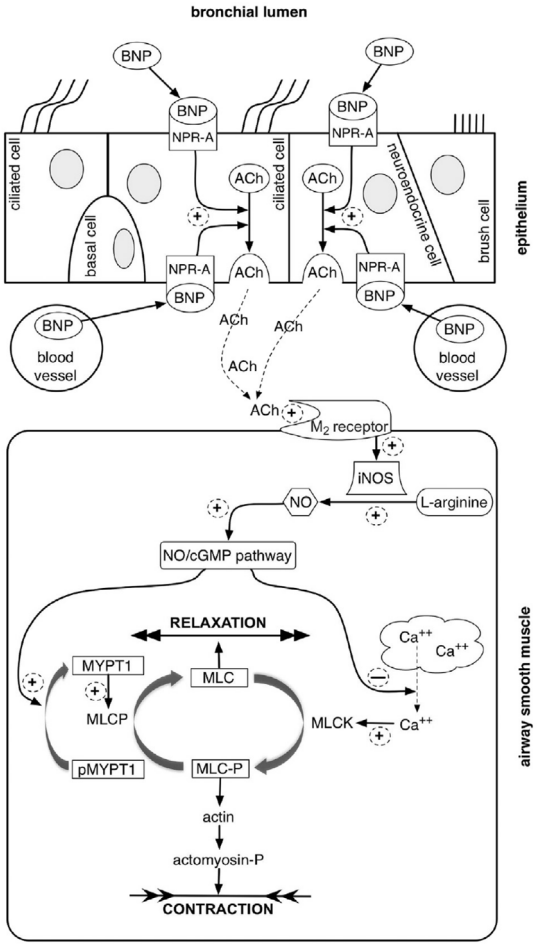


Inhaled RPL554 is an effective and well tolerated bronchodilator and anti-inflammatory drug and further studies will establish the full potential of this new drug for the treatment of patients with COPD

Inhaled BNP

- The **bronchorelaxant activity of BNP** is mediated by the interaction with the NPR-A localized at the level of bronchial epithelial cells. The inhalant administration of BNP should reduce the risk of hypotension.

- Epithelium integrity is an essential condition for the effectiveness of BNP, administered in combination with further bronchodilators in order to optimize the therapeutic approach



Calzetta L, et al. Intern J Cardiol 2016

Conclusions

- Drug therapy in COPD is aimed at reducing symptoms and future risk, independent on the level of obstruction
- Inhaled combination therapies are effective and safe and should be better tailored on the patients' risk(s)
- Additional pulmonary and extra-pulmonary drugs may be (or might be) delivered based on the individual's treatable trait(s)
- Further attention should be given to new agents with specific targets able to sinergistically potentiate desiderable effects