Bologna 18 settembre 2017

I DEVICE
DEI FARMACI RESPIRATORI:
QUALE RUOLO
NELLA SCELTA TERAPEUTICA?

NH Bologna
Hotel de la Gare
Piazza XX Settembre, 2

Asma e BPCO: le strategie terapeutiche

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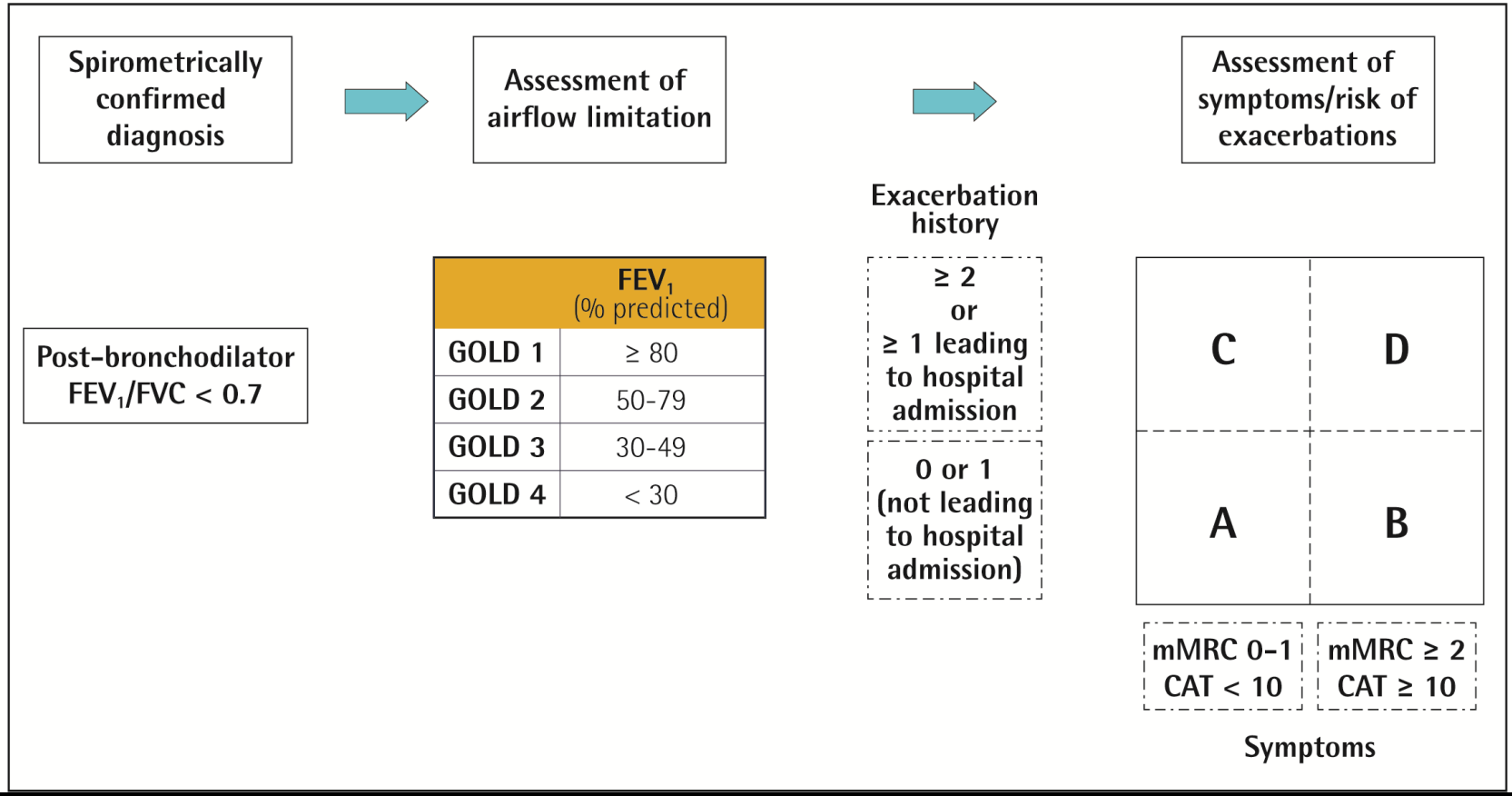
COPD Definition

- Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.

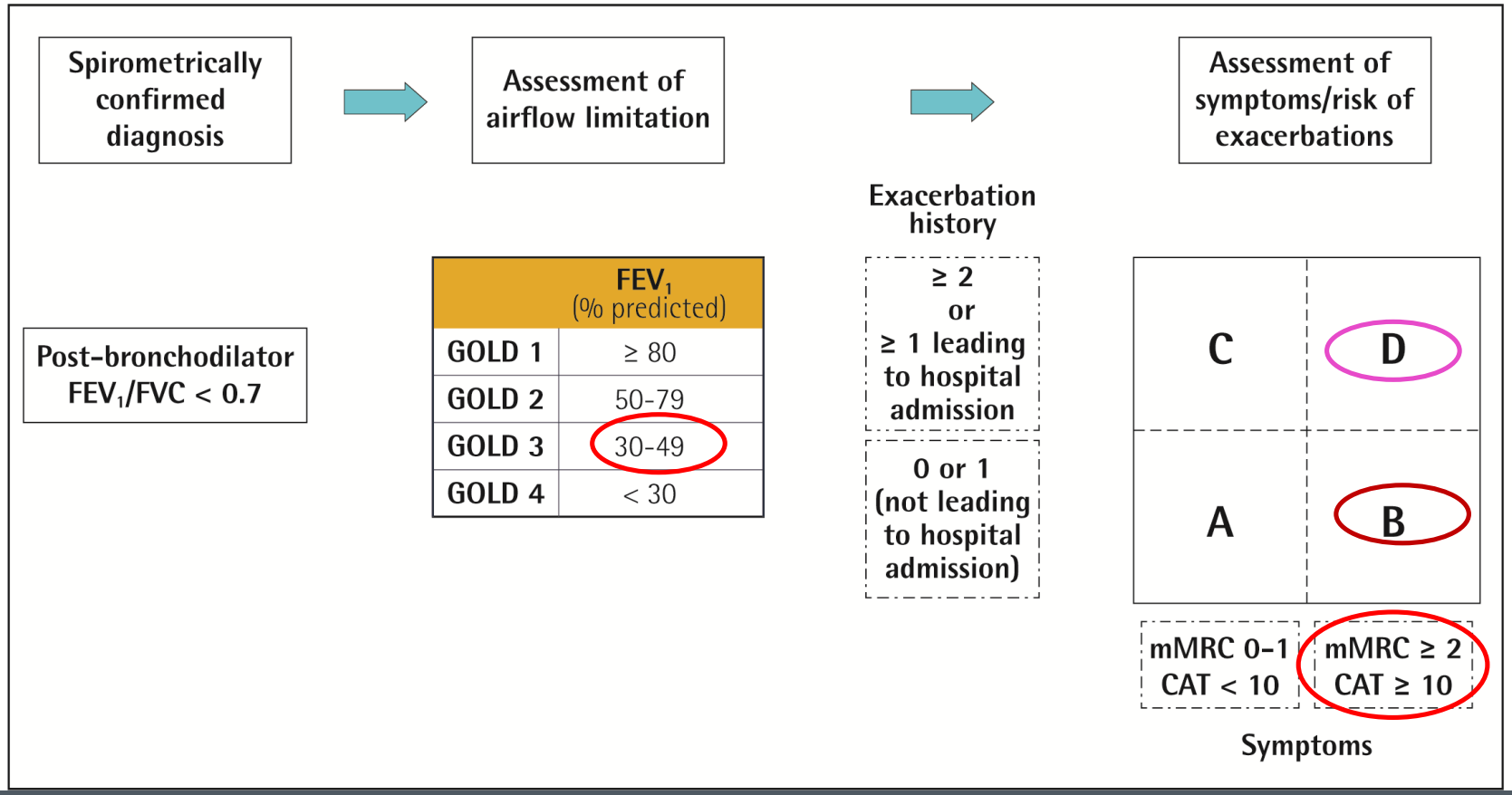
ABCD Assessment Tool

Figure 2.4. The refined ABCD assessment tool



ABCD Assessment Tool

Figure 2.4. The refined ABCD assessment tool



ABCD Assessment Tool

Figure 2.4. The refined ABCD assessment tool

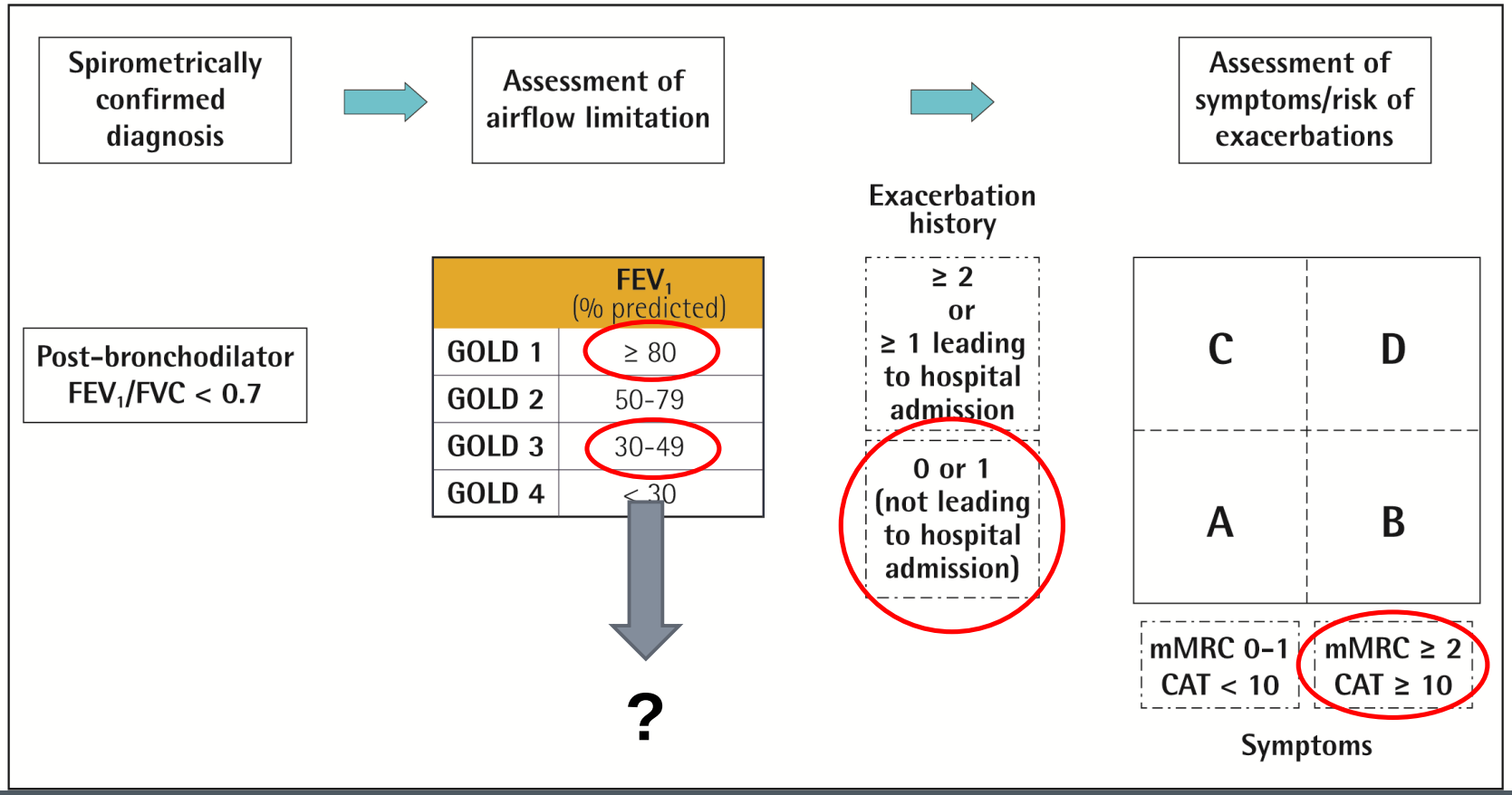
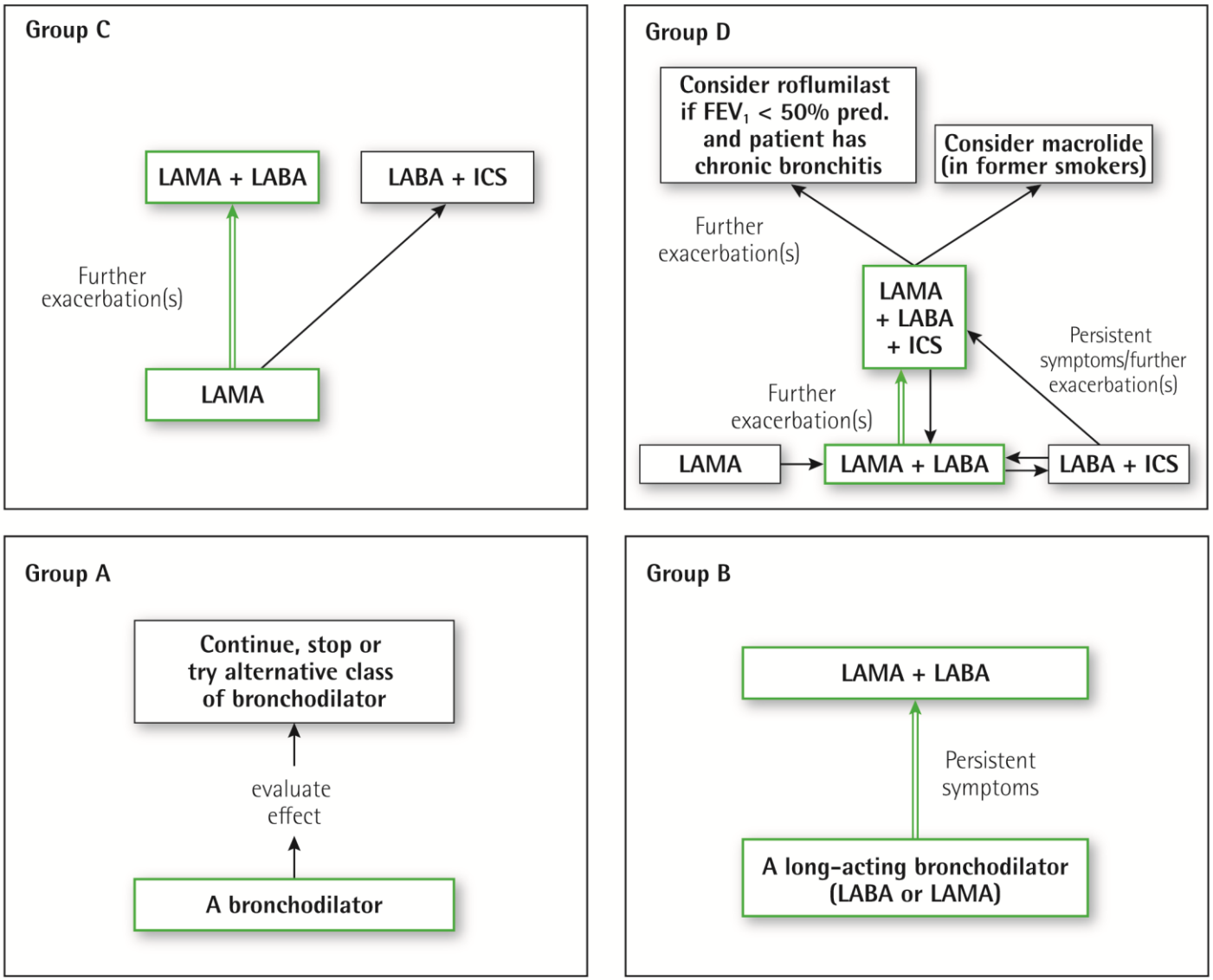


Figure 4.1. Pharmacologic treatment algorithms by GOLD Grade [highlighted boxes and arrows indicate preferred treatment pathways]



Preferred treatment =

In patients with a major discrepancy between the perceived level of symptoms and severity of airflow limitation, further evaluation is warranted.

The NEW ENGLAND JOURNAL of MEDICINE

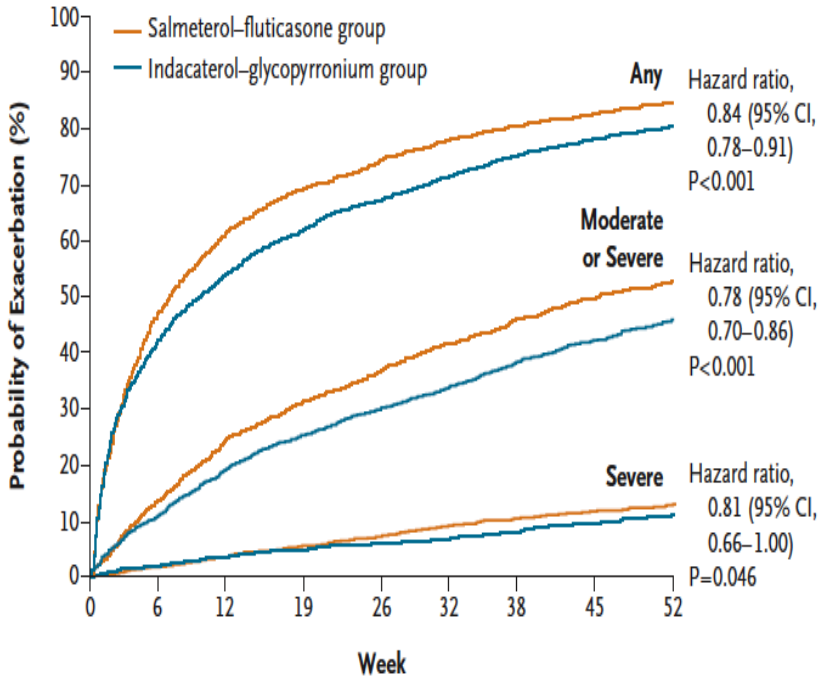
ORIGINAL ARTICLE

Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD

Jadwiga A. Wedzicha, M.D., Donald Banerji, M.D., Kenneth R. Chapman, M.D., Jørgen Vestbo, M.D., D.M.Sc., Nicolas Roche, M.D., R. Timothy Ayers, M.Sc., Chau Thach, Ph.D., Robert Fogel, M.D., Francesco Patalano, M.D., and Claus F. Vogelmeier, M.D., for the FLAME Investigators*

Table 1. Baseline Characteristics of the Patients.*

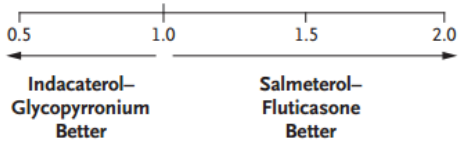
Characteristic	Indacaterol–Glycopyrronium Group (N=1680)	Salmeterol–Fluticasone Group (N=1682)	All Patients (N=3362)
Age — yr	64.6±7.9	64.5±7.7	64.6±7.8
Male sex — no. (%)	1299 (77.3)	1258 (74.8)	2557 (76.1)
Duration of COPD — yr	7.2±5.3	7.3±5.5	7.3±5.4
Use of inhaled glucocorticoids at screening — no. (%)	954 (56.8)	939 (55.8)	1893 (56.3)
Current smoker — no. (%)	664 (39.5)	669 (39.8)	1333 (39.6)
Severity of COPD — no. (%)†			
Group A	2 (0.1)	0	2 (0.1)
Group B	400 (23.8)	422 (25.1)	822 (24.4)
Group C	1 (0.1)	2 (0.1)	3 (0.1)
Group D	1265 (75.3)	1249 (74.3)	2514 (74.8)
Post-bronchodilator FEV_1 — liters	1.2±0.3	1.2±0.4	1.2±0.3
Post-bronchodilator FEV_1 — % of predicted value	44.0±9.5	44.1±9.4	44.1±9.5
Post-bronchodilator ratio of FEV_1 to FVC — %	41.7±9.8	41.5±9.9	41.6±9.9
Total score on the SGRQ-C‡	47.3±15.8	47.2±15.9	47.3±15.8



(2016)

LABA/LAMA vs ICS/LABA

Subgroup	Indacaterol–Glycopyrronium Group (no. of patients)	Salmeterol–Fluticasone Group (no. of patients)	Rate Ratio (95% CI)
Sex			
Male	1271	1238	0.88 (0.81–0.96)
Female	380	418	0.88 (0.76–1.02)
Race			
White	1286	1283	0.89 (0.82–0.96)
Asian	301	308	0.88 (0.74–1.05)
Other	64	65	0.90 (0.62–1.29)
Smoking status at screening			
Former smoker	1004	998	0.92 (0.83–1.01)
Current smoker	647	658	0.83 (0.74–0.92)
Severity of airflow limitation			
Moderate	557	557	0.93 (0.82–1.06)
Severe	962	975	0.84 (0.76–0.92)
Very severe	132	124	0.94 (0.72–1.22)
Severity of COPD			
Group B	398	417	0.98 (0.85–1.14)
Group D	1252	1243	0.85 (0.78–0.92)
COPD exacerbations during the previous year			
1 Exacerbation	1329	1335	0.87 (0.81–0.95)
≥2 Exacerbations	321	320	0.89 (0.76–1.05)
Inhaled glucocorticoid use at screening			
No use	710	729	0.88 (0.79–0.98)
Use	941	927	0.88 (0.80–0.97)
LABA use at screening			
No use	540	542	0.91 (0.81–1.04)
Use	1111	1114	0.86 (0.79–0.94)
LABA–inhaled glucocorticoid use at screening			
No use	879	889	0.88 (0.80–0.97)
Use	772	767	0.88 (0.79–0.97)
LAMA use at screening			
No use	662	643	0.91 (0.81–1.02)
Use	989	1013	0.86 (0.78–0.94)
Overall	1651	1656	0.88 (0.82–0.94)



N ENGL J MED 375;9 NEJM.ORG SEPTEMBER 1, 2016

TO THE EDITOR: The majority of patients recruited into the FLAME trial met the Global Initiative for Chronic Obstructive Lung Disease guidelines group D criterion of low FEV_1, whereas only a minority (19.3%) met the frequent-exacerbation criterion of two or more exacerbations in the previous year.[1] Patients with frequent exacerbations and high eosinophil counts are more likely to benefit from inhaled-glucocorticoid–containing therapy than from therapies without inhaled glucocorticoids.[2,3] The FLAME trial shows a significant difference between long-acting beta-agonist (LABA)–long-acting muscarinic antagonist treatment and LABA–inhaled glucocorticoid treatment in reducing exacerbations in patients with one exacerbation, but not in those with two or more exacerbations, in the previous year (Fig. 3 of the article, and Fig. S6B in the Supplementary Appendix of the article). We wonder about the efficacy of the tested treatments in patients with frequent exacerbations (two or more in the previous year) when stratified according to baseline blood eosinophil levels.

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A2318 FLAME

Wedzicha JA et al., N Engl J Med 2016

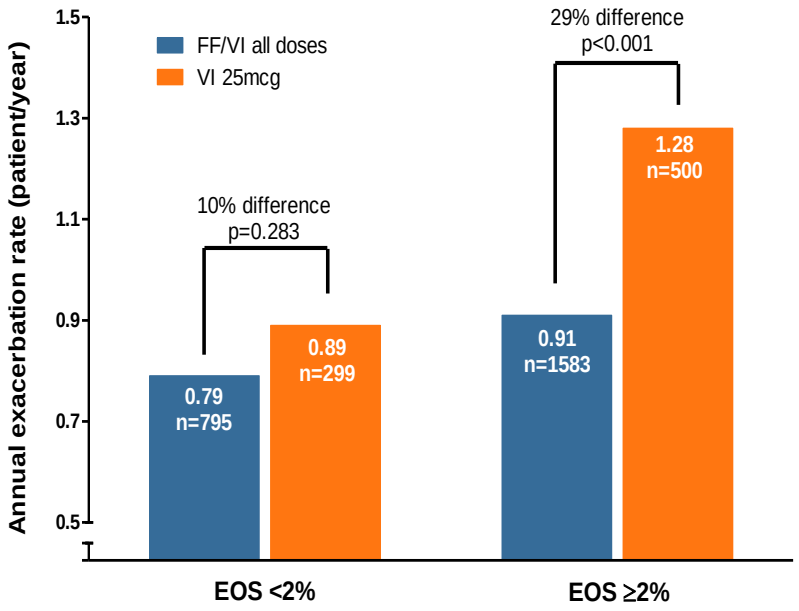
Blood eosinophil count and exacerbation risk in patients with COPD

Of 64,847 identified patients with COPD, 8318 were eligible for inclusion in the study (56% men and mean±SD age of 70±10 years). Modified Medical Research Council (mMRC) scores were available for 6660 of these patients, for determining GOLD groups [6]. During the follow-up year, 40% of patients with reference eosinophil counts, 42% with elevated counts, and 43% with low counts experienced ⩾1 COPD exacerbations, whereas 16%, 18%, and 17%, respectively, experienced ⩾2 COPD exacerbations. Overall, patients with elevated blood eosinophil counts (8.9%) had a 13% higher exacerbation rate during the following year than patients in the reference group (87.7%). When investigating this association in different patient subgroups, we found a significant difference between ex-smokers and current smokers, with ex-smokers showing the higher exacerbation rate in patients with elevated blood eosinophil counts (table 1). We further compared exacerbation rates in four different patient subgroups, defined by smoking

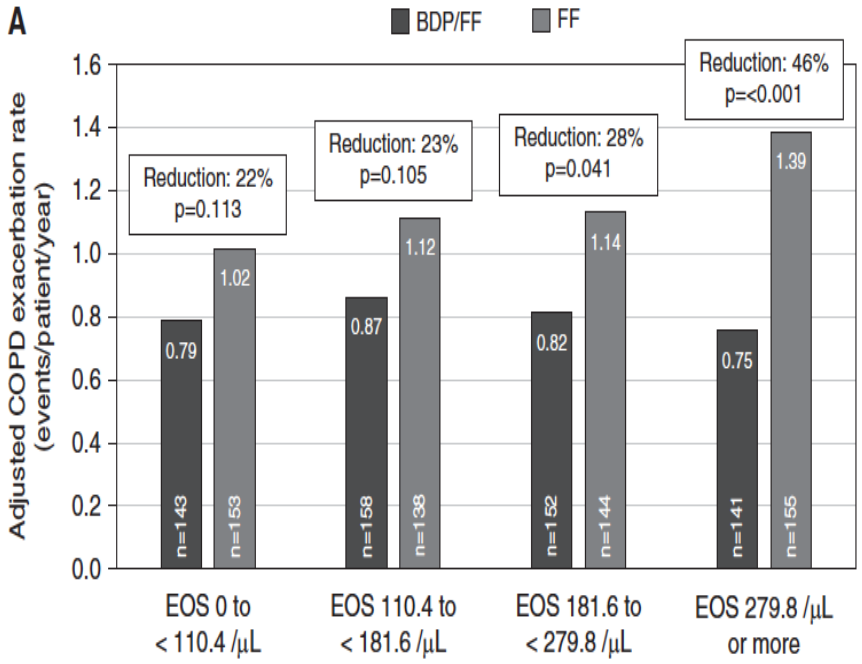
(Kerhof et al. ERJ 2017)

Eosinophils in blood and response to ICS treatment in COPD

Exacerbations (per annum) by treatment and EOS level at screening

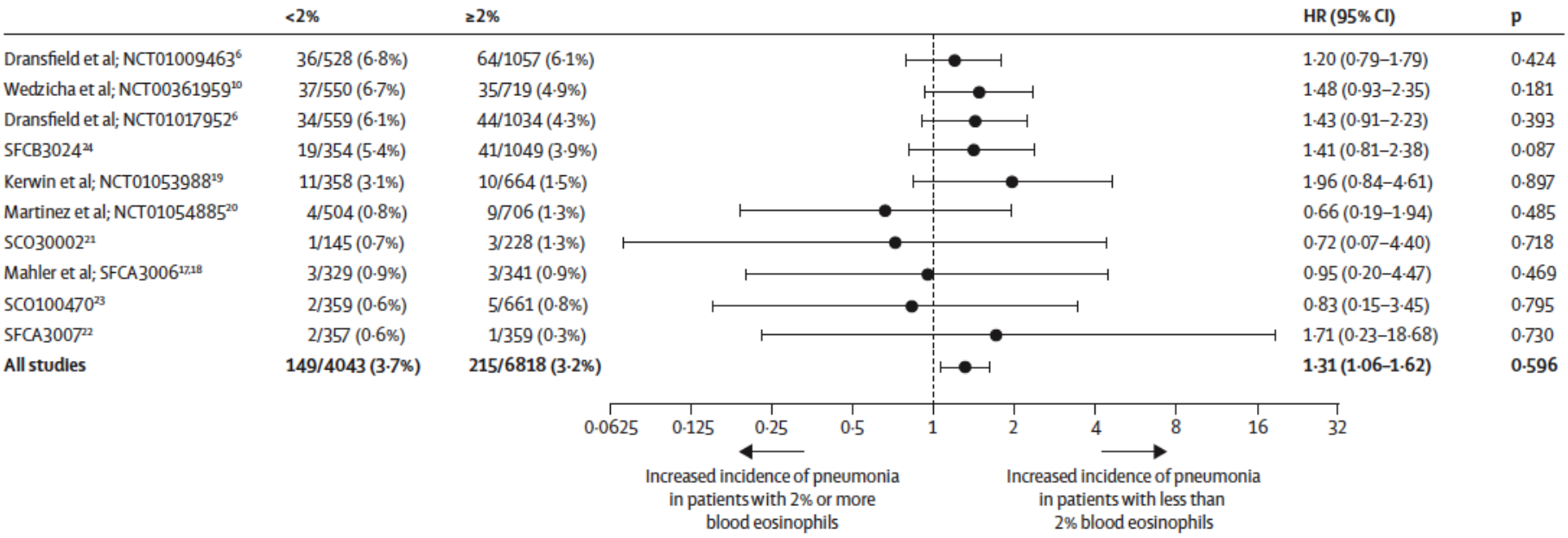


Pascoe S, Lancet Resp Med 2015



(Siddiqui et al. AJRCCM 2015)

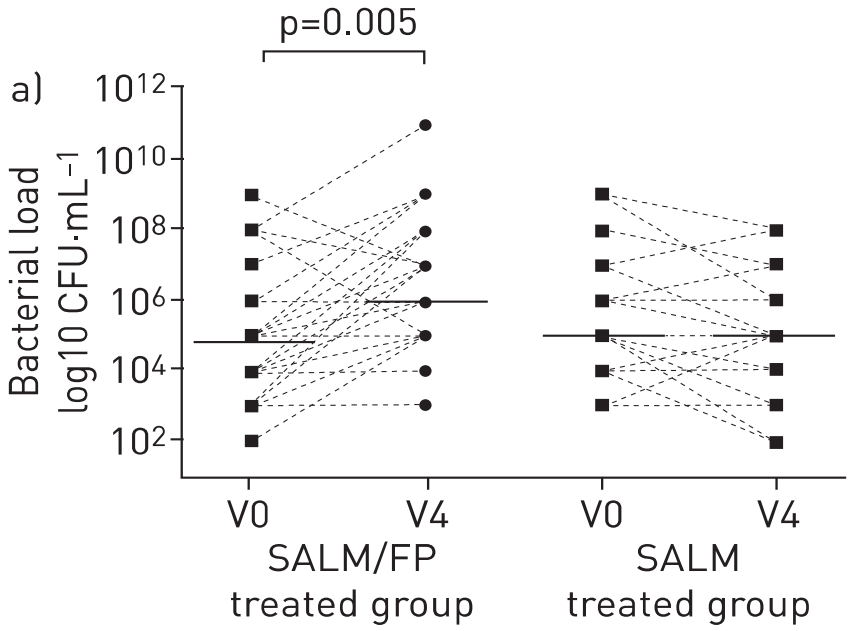
Blood eosinophil count and pneumonia risk in patients with chronic obstructive pulmonary disease: a patient-level meta-analysis

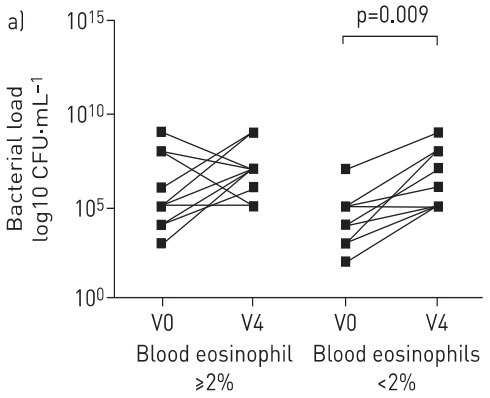


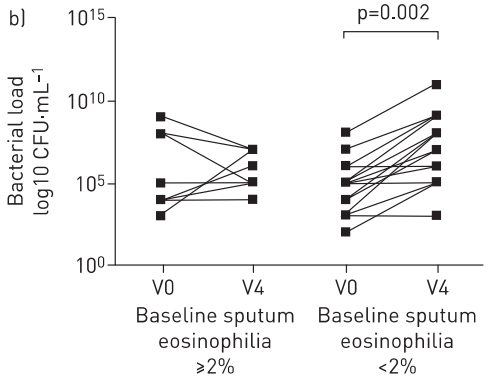
(Pavord et al. Lancet Respir Med 2016)

Long-term effects of inhaled corticosteroids on sputum bacterial and viral loads in COPD

Marco Contoli[1], Alessia Pauletti[1], Maria Rita Rossi[2], Antonio Spanevello[3], Paolo Casolari[1], Andrea Marcellini[1], Giacomo Forini[1], Giulia Gnesini[1], Brunilda Marku[1], Neil Barnes[4,5], Andrea Rizzi[6], Giacomo Curradi[6], Gaetano Caramori[1], Paolo Morelli[2] and Alberto Papi[1]

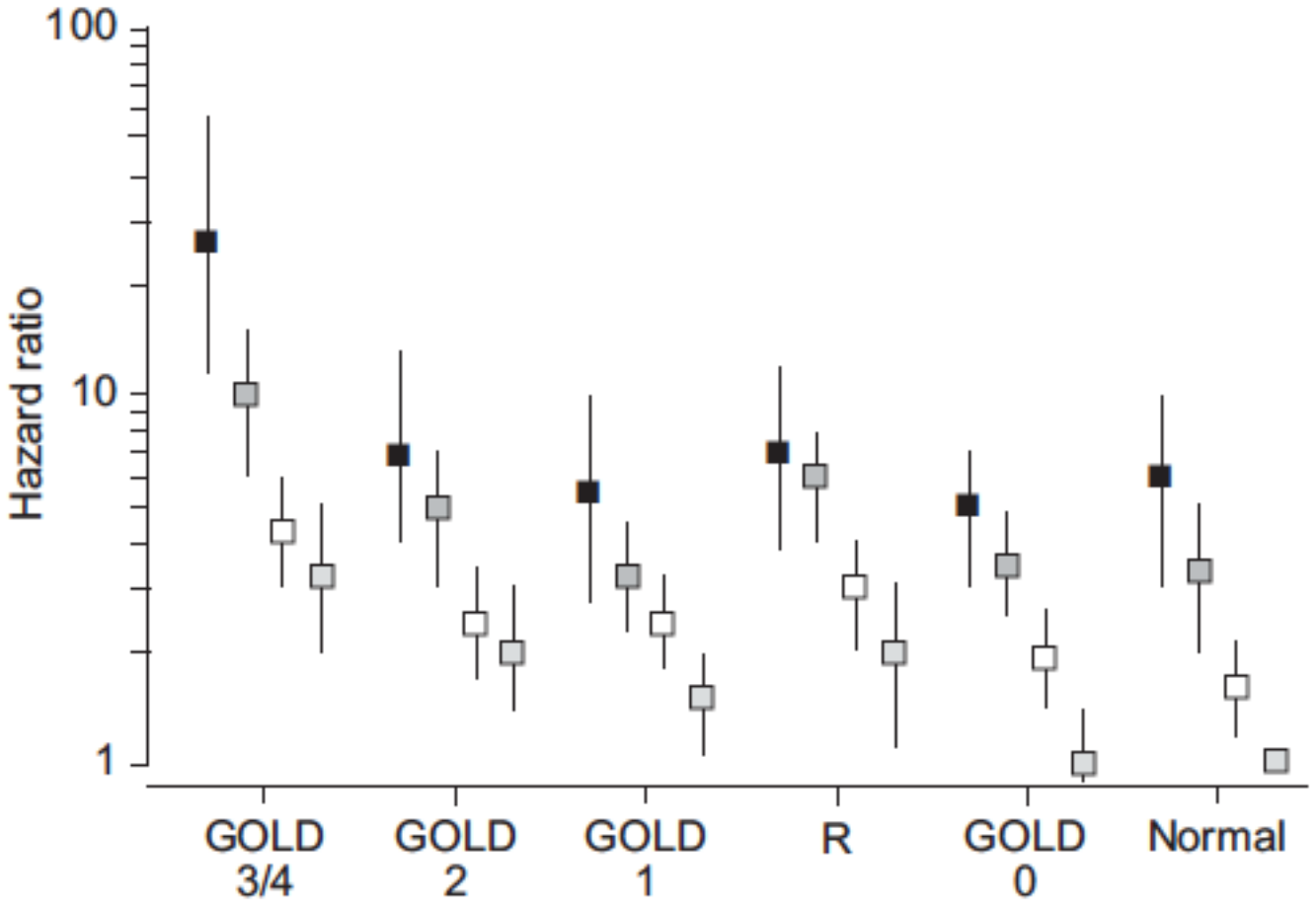






(ERJ 2017 in press)

Comorbidities and mortality



(Mannino et al. ERJ 2008)

COPD and Comorbidities

OVERALL KEY POINTS

- COPD often coexists with other diseases (comorbidities) that may have a significant impact on disease course.
- In general, the presence of comorbidities should not alter COPD treatment and comorbidities should be treated per usual standards regardless of the presence of COPD.
- Lung cancer is frequently seen in patients with COPD and is a main cause of death.
- Osteoporosis and depression/anxiety are frequent, important comorbidities in COPD, are often under-diagnosed, and are associated with poor health status and prognosis.
- Gastroesophageal reflux (GERD) is associated with an increased risk of exacerbations and poorer health status.
- Cardiovascular diseases are common and important comorbidities in COPD.

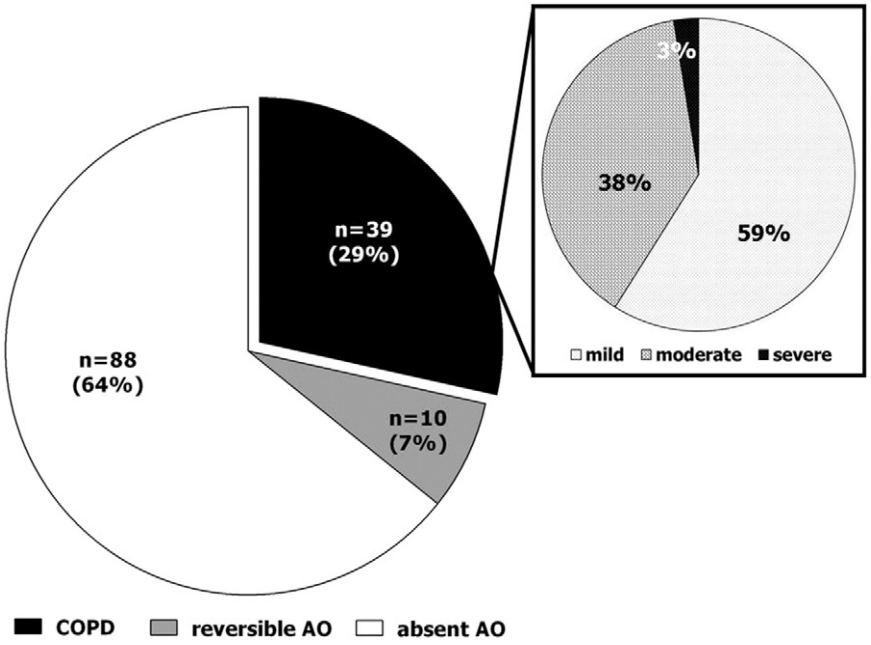
Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Predischarge screening for chronic obstructive pulmonary disease in patients with acute coronary syndrome and smoking history

Gianluca Campo, MD [a,b,*], Rita Pavasini, MD [a], Carlo Barbetta, MD [c], Elisa Maietti, MSc [d], Susanna Mascetti, MD [c], Simone Biscaglia, MD [a], Fatima Zaraket, MD [a], Giosafat Spitaleri, MD [a], Francesco Gallo, MD [a], Elisabetta Tonet, MD [a], Alberto Papi, MD, PhD [c], Roberto Ferrari, MD, PhD [a,b,e], Marco Contoli, MD, PhD [c]

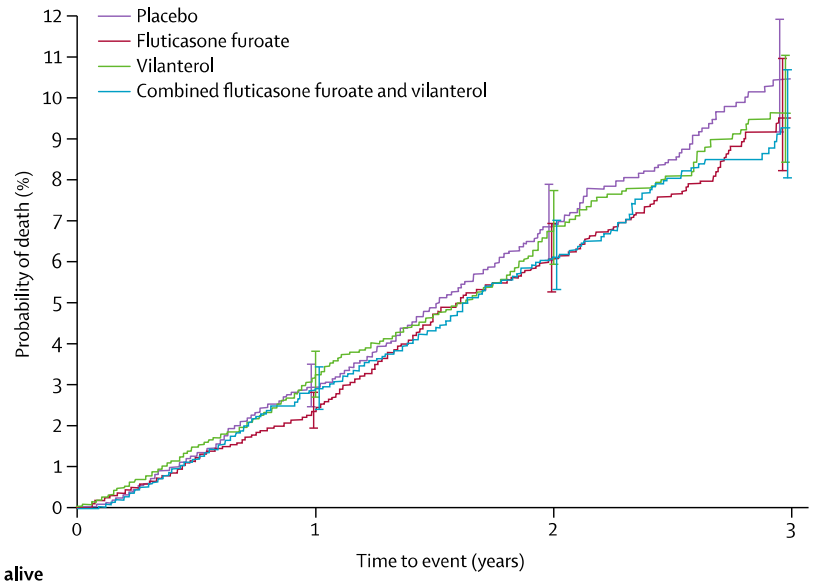


(2016)

Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial

Jørgen Vestbo, Julie A Anderson, Robert D Brook, Peter M A Calverley, Bartolome R Celli, Courtney Crim, Fernando Martinez, Julie Yates, David E Newby, on behalf of the SUMMIT Investigators

	Placebo (n=4111)	Fluticasone furoate (n=4135)	Vilanterol (n=4118)	Combination therapy (n=4121)
Age (years)	65 (8)	65 (8)	65 (8)	65 (8)
Women	1040 (25%)	1082 (26%)	1065 (26%)	1009 (24%)
Race				
White	3328 (81%)	3358 (81%)	3339 (81%)	3332 (81%)
Asian	682 (17%)	683 (17%)	680 (17%)	679 (16%)
Other	101 (2%)	94 (2%)	99 (2%)	110 (3%)
Body-mass index (kg/m²)	28 (6)	28 (6)	28 (6)	28 (6)
Current smokers	1936 (47%)	1945 (47%)	1929 (47%)	1868 (45%)
Smoking history (pack-years)	41 (25)	41 (24)	41 (24)	41 (24)
Post-bronchodilator FEV_1 (L)	1·70 (0·40)	1·70 (0·41)	1·70 (0·40)	1·70 (0·40)
Predicted post-bronchodilator FEV_1 (%)	59·7 (6·1)	59·6 (6·1)	59·7 (6·1)	59·7 (6·1)
FEV_1 reversibility (as a % of pre-bronchodilator FEV_1)	8·4% (12·1)	7·9% (11·7)	8·3% (12·2)	8·0% (11·8)
Pre-study COPD therapy				
Long-acting β agonist	1417 (34%)	1432 (35%)	1464 (36%)	1456 (35%)
Long-acting muscarinic agonist	659 (16%)	619 (15%)	634 (15%)	638 (15%)
Inhaled corticosteroid	1349 (33%)	1369 (33%)	1374 (33%)	1394 (34%)
Pre-study exacerbations in 12 months before study				
0	2447 (60%)	2546 (62%)	2500 (61%)	2528 (61%)
1	1044 (25%)	990 (24%)	988 (24%)	998 (24%)
2+	620 (15%)	599 (14%)	630 (15%)	595 (14%)
Cardiovascular inclusion criteria*				
Manifest disease				
Coronary artery disease	2103 (51%)	2119 (51%)	2044 (50%)	2113 (51%)
Peripheral arterial disease	766 (19%)	755 (18%)	817 (20%)	807 (20%)
Previous stroke	404 (10%)	418 (10%)	387 (9%)	386 (9%)
Previous myocardial infarction	658 (16%)	664 (16%)	722 (18%)	730 (18%)
Diabetes with target organ disease	374 (9%)	355 (9%)	377 (9%)	397 (10%)
At risk				
Hypercholesterolaemia	2112 (66%)	2051 (65%)	2191 (67%)	2125 (66%)
Hypertension	2861 (89%)	2835 (89%)	2900 (89%)	2882 (90%)
Diabetes mellitus	850 (27%)	870 (27%)	874 (27%)	886 (28%)
Peripheral arterial disease	279 (9%)	264 (8%)	301 (9%)	310 (10%)



Number alive				
Placebo	4111	3465	1715	469
Fluticasone furoate	4135	3499	1734	490
Vilanterol	4118	3466	1734	486
Combined fluticasone furoate and vilanterol	4121	3484	1718	485

(2016)

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

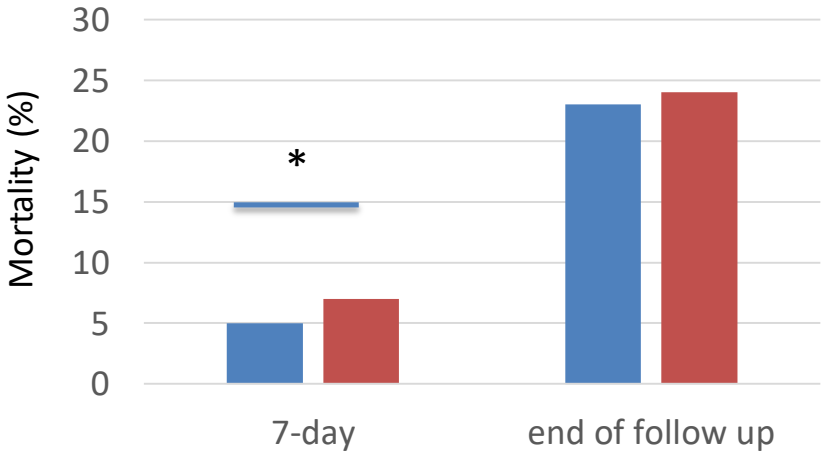
Inhaled corticosteroid/long-acting bronchodilator treatment mitigates STEMI clinical presentation in COPD patients

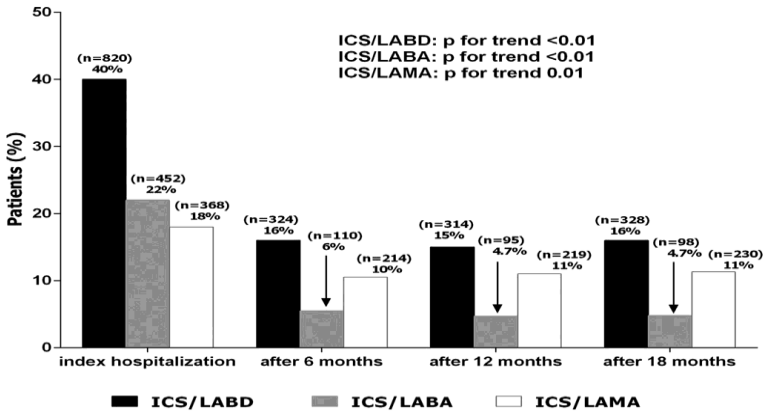
Marco Contoli [a,1], Gianluca Campo [b,c,1], Rita Pavasini [b], Irene Marchi [a], Alessia Pauletti [a], Cristina Balla [b], Antonio Spanevello [d], Roberto Ferrari [b,c,e], Alberto Papi [a,*]

Table 2
Clinical presentation of ST-segment elevation myocardial infarction (STEMI).

	COPD patients (n = 2032)	No ICS/LABD (n = 1212)	ICS/LABD (n = 820)	p
Pulmonary oedema no. (%)	353 (17)	237 (20)	116 (14)	0.009
Cardiogenic shock no. (%)	236 (12)	161 (13)	75 (9)	0.01
IABP use no. (%)	136 (7)	96 (8)	40 (5)	0.02
Heart rate (bpm)	78 ± 18	78 ± 18	77 ± 19	0.7
Systolic blood pressure (mm Hg)	125 ± 28	123 ± 30	127 ± 28	0.02

COPD: chronic obstructive pulmonary disease. ICS: inhaled corticosteroid. LABD: long-acting bronchodilator; IABP: intra-aortic balloon pump.





(2017)

Definition of asthma

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation.

It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

What is known about asthma?

- Asthma is a common and potentially serious chronic disease that can be controlled but not cured
- Asthma can be effectively treated
- When asthma is well-controlled, patients can
  - ✓ Avoid troublesome symptoms during the day and night
  - ✓ Need little or no reliever medication
  - ✓ Have productive, physically active lives
  - ✓ Have normal or near-normal lung function
  - ✓ Avoid serious asthma flare-ups (also called exacerbations, or severe attacks)

GINA assessment of asthma control

A. Symptom control

Level of asthma symptom control

In the past 4 weeks, has the patient had:		Well-controlled	Partly controlled	Uncontrolled
• Daytime asthma symptoms more than twice a week?	Yes ❑ No ❑	None of these	1-2 of these	3-4 of these
• Any night waking due to asthma?	Yes ❑ No ❑			
• Reliever needed for symptoms* more than twice a week?	Yes ❑ No ❑			
• Any activity limitation due to asthma?	Yes ❑ No ❑			

B. Risk factors for poor asthma outcomes

- Assess risk factors at diagnosis and periodically
- Measure FEV_1 at start of treatment, after 3 to 6 months of treatment to record the patient's personal best, then periodically for ongoing risk assessment

ASSESS PATIENT'S RISKS FOR:

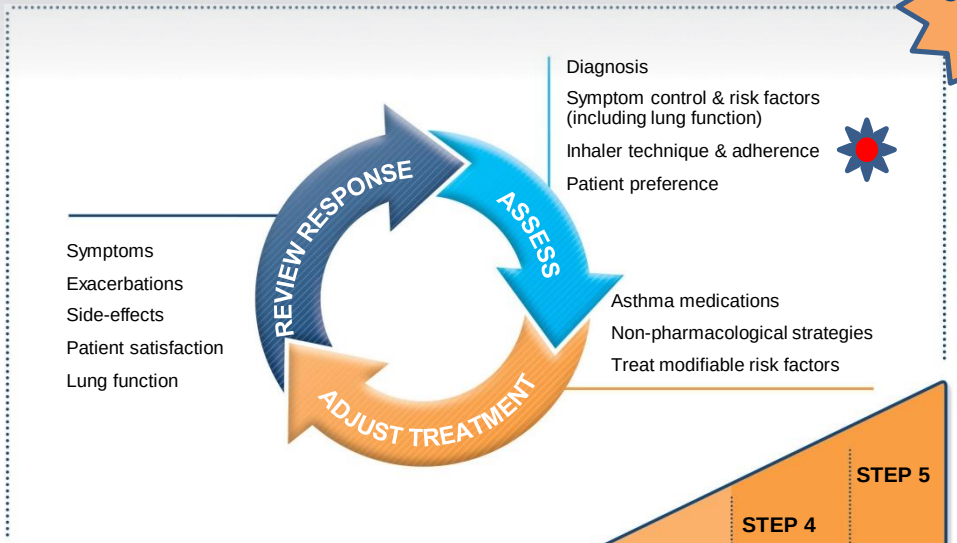
- Exacerbations
- Fixed airflow limitation
- Medication side-effects

Assessing asthma severity

- How?
  - Asthma severity is assessed retrospectively from the level of treatment required to control symptoms and exacerbations
- When?
  - Assess asthma severity after patient has been on controller treatment for several months
  - Severity is not static – it may change over months or years, or as different treatments become available
- Categories of asthma severity
  - *Mild asthma:* well-controlled with Steps 1 or 2 (as-needed SABA or low dose ICS)
  - *Moderate asthma:* well-controlled with Step 3 (low-dose ICS/LABA)
  - *Severe asthma:* requires Step 4/5 (moderate or high dose ICS/LABA ± add-on), or remains uncontrolled despite this treatment

Stepwise approach to control asthma symptoms and reduce risk

UPDATED 2017



	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER CHOICE		Low dose ICS	Low dose ICS/LABA**	Med/high ICS/LABA	Refer for add-on treatment e.g. tiotropium,*† anti-IgE, anti-IL5*
Other controller options	*Consider low dose ICS*	*Leukotriene receptor antagonists (LTRA) Low dose theophylline**	*Med/high dose ICS Low dose ICS+LTRA (or + theoph*)*	*Add tiotropium*† High dose ICS + LTRA (or + theoph*)*	*Add low dose OCS*
RELIEVER	As-needed short-acting beta$_2$-agonist (SABA)		As-needed SABA or low dose ICS/formoterol#		

REMEMBER TO...

- Provide guided self-management education (self-monitoring + written action plan + regular review)
- Treat modifiable risk factors and comorbidities, e.g. smoking, obesity, anxiety
- Advise about non-pharmacological therapies and strategies, e.g. physical activity, weight loss, avoidance of sensitizers where appropriate
- Consider stepping up if … uncontrolled symptoms, exacerbations or risks, but check diagnosis, inhaler technique and adherence first
- Consider adding SLIT in adult HDM-sensitive patients with allergic rhinitis who have exacerbations despite ICS treatment, provided FEV1 is >70% predicted
- Consider stepping down if … symptoms controlled for 3 months + low risk for exacerbations. Ceasing ICS is not advised.

Cutoff in IgE-mediated asthma

		IgE levels (IU/mL) (consider weight)	**Reference**
Anti IgE	**Omalizumab**	30-1300	Humbert et al. JACI in practice 2014 (Review)

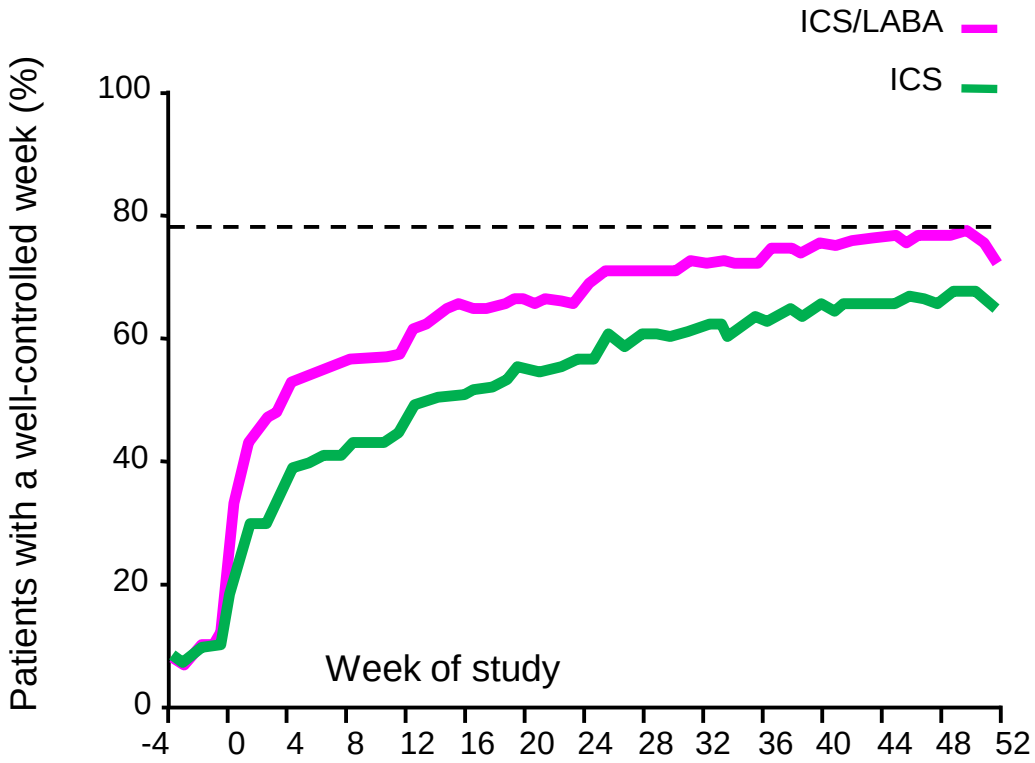
Cutoff in eosinophilic asthma

		Eosinophil level (cells/µl)	**Reference**
Anti IL-5	**Reslizumab**	≥400	Bjermer L, 3081 study (2016), Castro M, 3082 and 3083 study (2015)
	Mepolizumab	≥ 300	Pavord ID, DREAM study (2012)
		≥ 150 at screening or >300 last year	Ortega HG, MENSA study (2014) Bel H, SIRIUS study (2014)
Anti IL-5R	**Benralizumab**	≥300	FitzGerald JM, CALIMA study (2016) Bleeker ER, SIROCCO study (2016)
Anti IL-13	**Lebrikizumab**	≥ 300	Hanania NA, LAVOLTA I and II study (2016)
Anti IL-4/13	**Dupilumab**	≥ 300	Wenzel S, N Engl J Med 2013 (IIa phase)

Inhaled treatment regimens

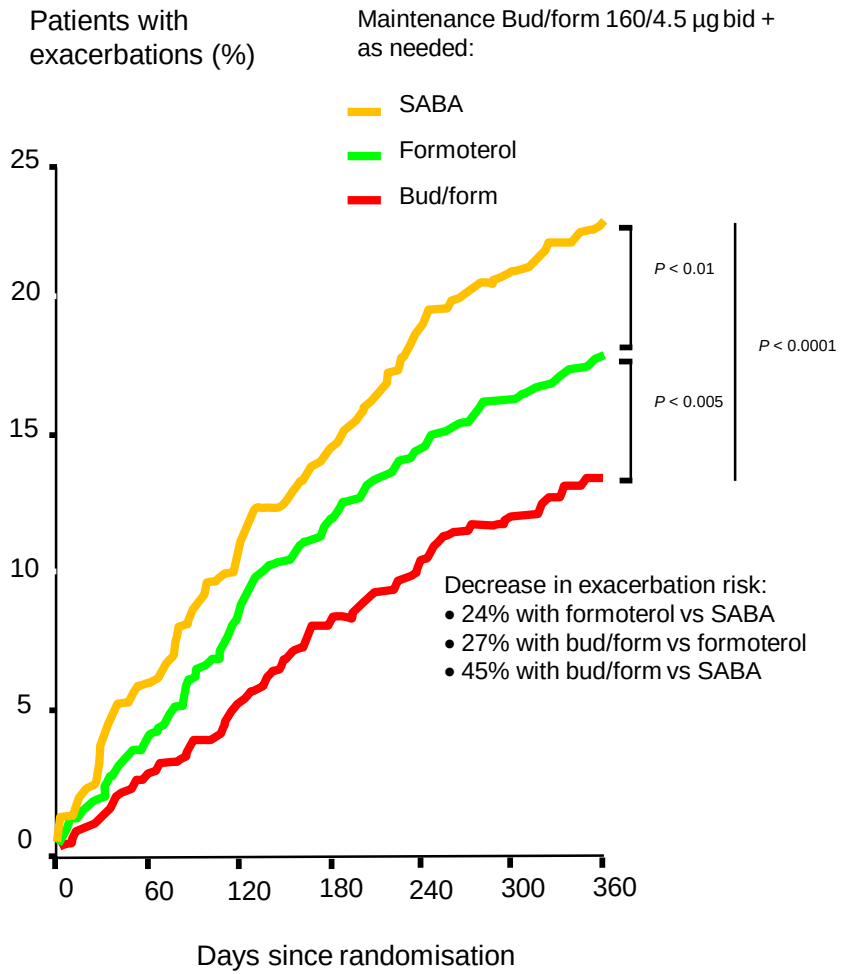
Can guideline-defined asthma control be achieved?

The Gaining Optimal Asthma ControL study

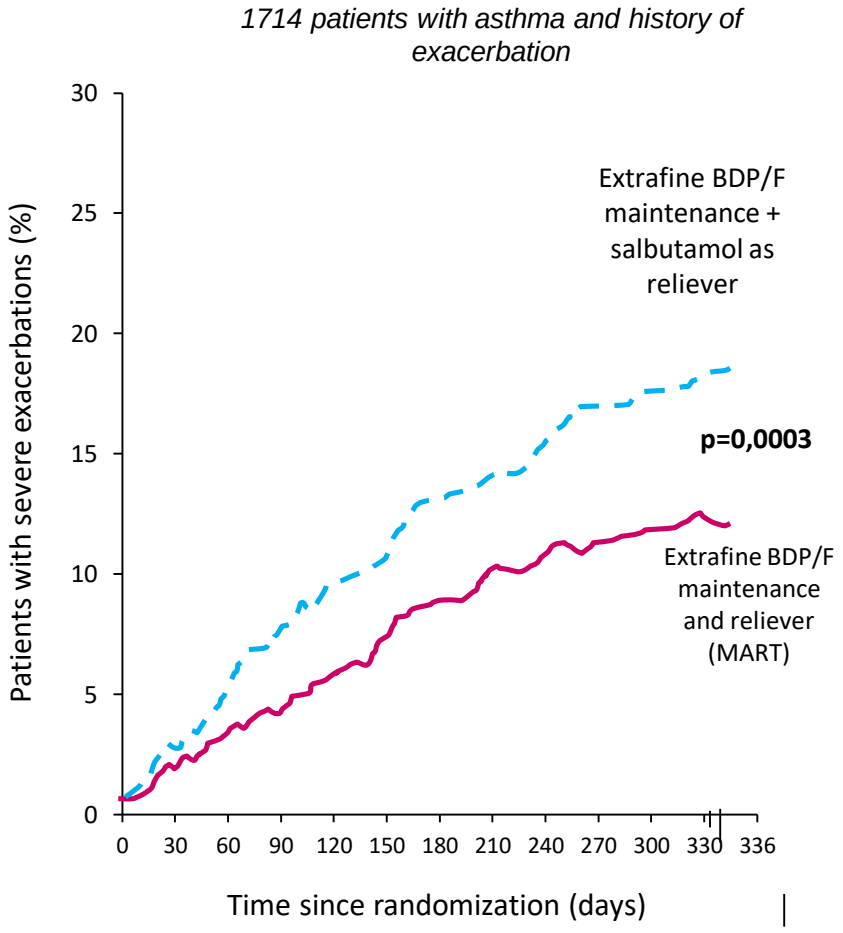


(Bateman et al. AJRCCM 2004)

SMART & MART



Rabe KF, et al. Lancet 2006

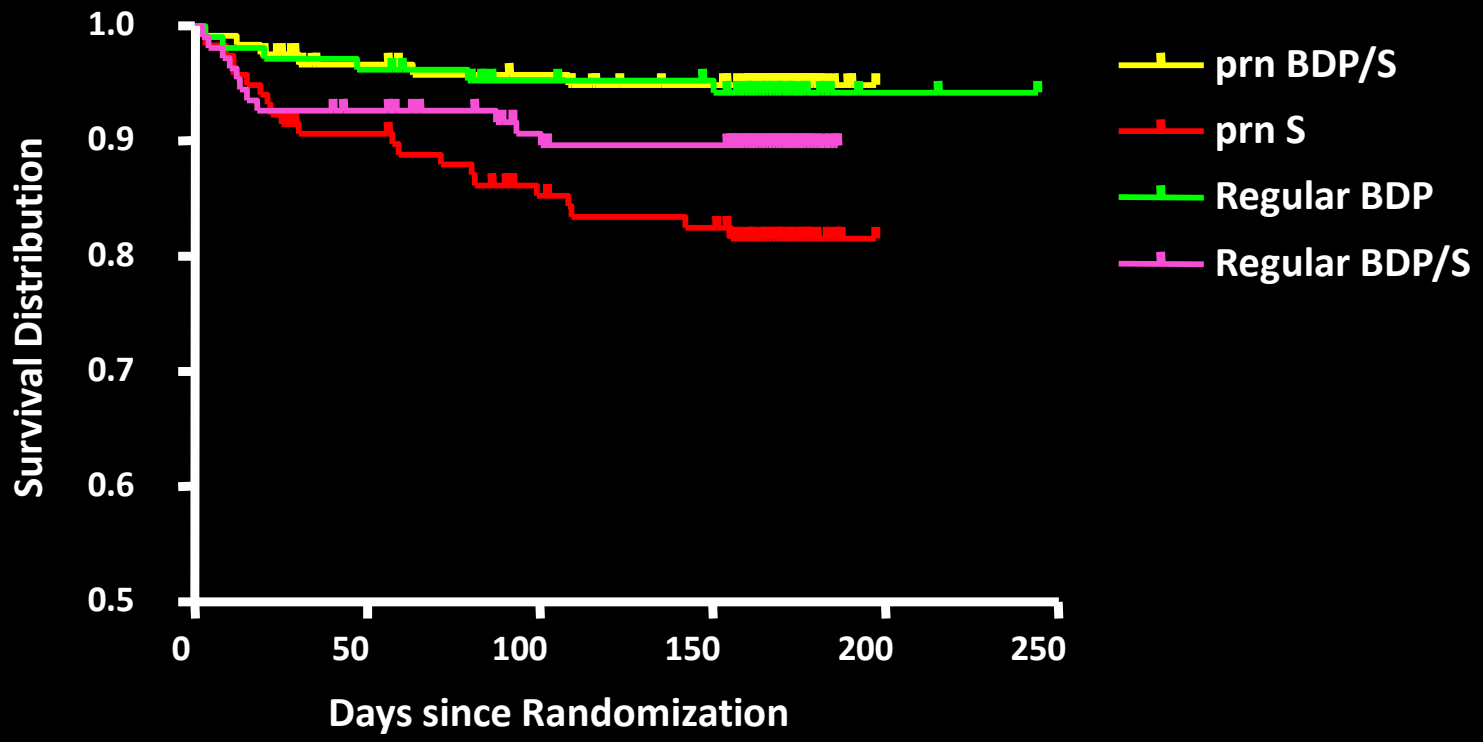


Papi et al, The Lancet Respir Med 2013

Symptom driven therapy

The NEW ENGLAND JOURNAL of MEDICINE

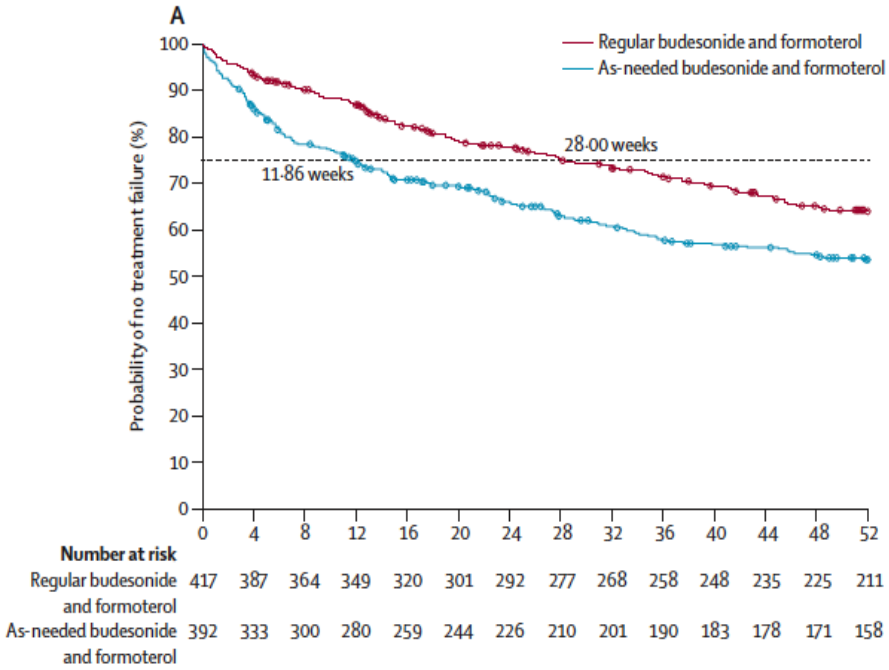
Rescue Use of Beclomethasone and Albuterol in a Single Inhaler for Mild Asthma



Papi A, Canonica GW, Maestrelli P, Paggiaro P, Olivieri O, Pozzi E, Crimi N, Vignola AM, Morelli P, Nicolini G, Fabbri LM and the BEST Study Group. N Engl J Med 2007;356:2040-52

Regular versus as-needed budesonide and formoterol combination treatment for moderate asthma: a non-inferiority, randomised, double-blind clinical trial

Alberto Papi, Brunilda Marku*, Nicola Scichilone, Piero Maestrelli, Pierluigi Paggiaro, Marina Saetta, Stefano Nava, Ilenia Folletti, Giuseppina Bertorelli, Stefano Bertacco, Marco Contoli, Mario Plebani, Maria Pia Foschino Barbaro, Antonio Spanevello, Maria Aliani, Marco Pannacci, Paolo Morelli, Bianca Beghé†, Leonardo M Fabbri†, for the AIFASMA Study Group‡*



	As-needed budesonide and formoterol group (n=394)	Regular budesonide and formoterol group (n=423)	p value
Admission to hospital	0	3 (1%)	0·250
Treatment stopped for safety reasons (physician's judgment)	24 (6%)	23 (5%)	0·688
Refusal to continue because of patient dissatisfaction with treatment	6 (2%)	4 (1%)	0·534
Two episodes of nocturnal awakenings on 2 consecutive days	82 (21%)	44 (10%)	<0·0001
Unscheduled medical visit for asthma worsening	6 (2%)	8 (2%)	0·685
Use of rescue medication	17 (4%)	18 (4%)	0·967
Use of systemic corticosteroids or inhaled corticosteroids for asthma worsening	51 (13%)	59 (14%)	0·674
Use of systemic corticosteroids for asthma worsening	31 (8%)	31 (7%)	0·771
Use of inhaled corticosteroids for asthma worsening	20 (5%)	28 (7%)	0·349

Data are n (%).

Table 3: **Reasons for treatment failure in the intention-to-treat population**

(2014)

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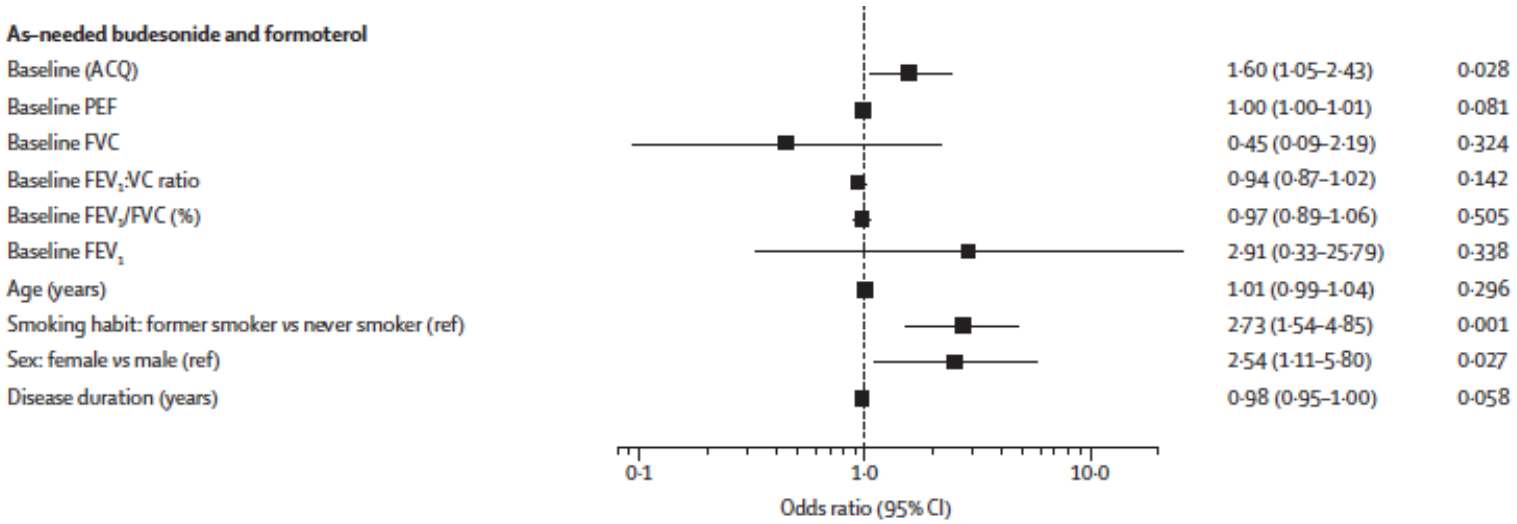


(2014)

SOCIETÀ ITALIANA DI PNEUMOLOGIA

Bologna 18 settembre 2017

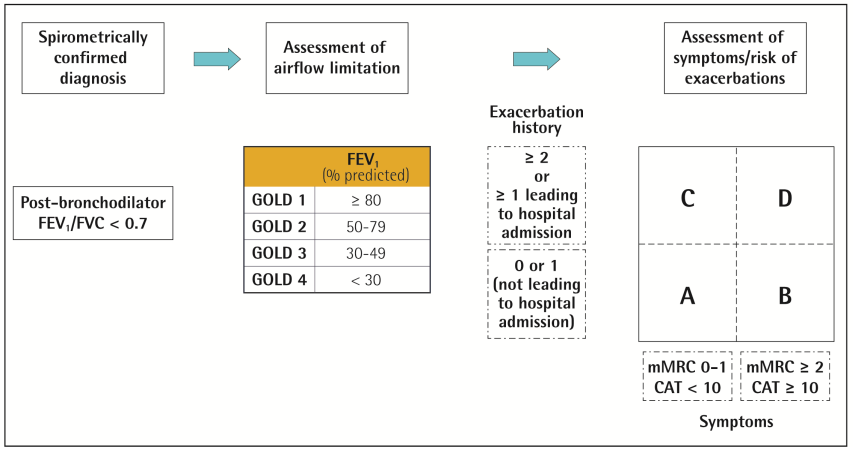
I DEVICE
DEI FARMACI RESPIRATORI:
QUALE RUOLO
NELLA SCELTA TERAPEUTICA?

NH Bologna
Hotel de la Gare
Piazza XX Settembre, 2

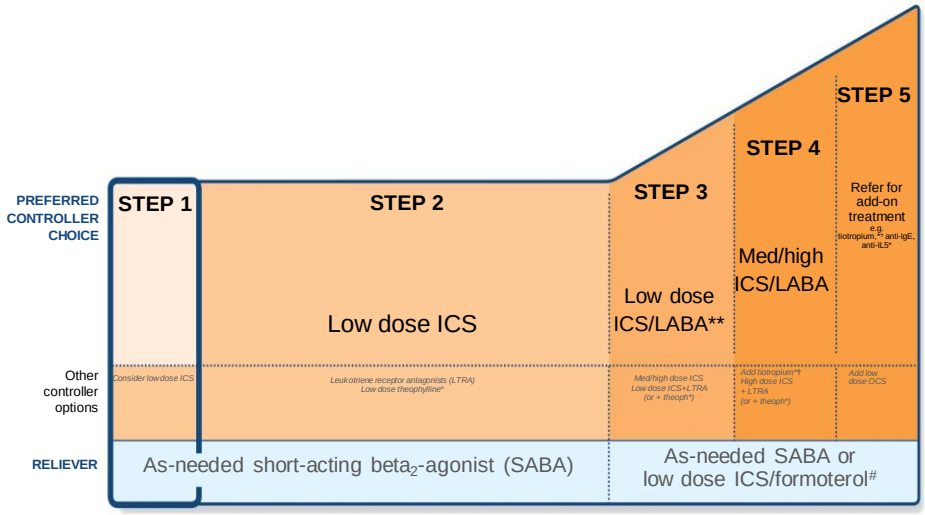
Asma e BPCO: le strategie terapeutiche

BPCO

Figure 2.4. The refined ABCD assessment tool



ASMA



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