COPD Phenotypes

Present or Future ?

Outline

- Need for phenotyping
- Eosinophilic COPD & Frequent exacerbator phenotype
  - Specific biologics – Mepolizumab
- Role of LABD (LAMA Vs LABA) /ICS/NAC/Roflumilast/Antibiotics
- Spanish COPD guidelines (based on clinical phenotypes)
- Characteristics of COPD phenotypes – population based studies
- GOLD Vs clinical phenotypes of Spanish guidelines
- Future -??

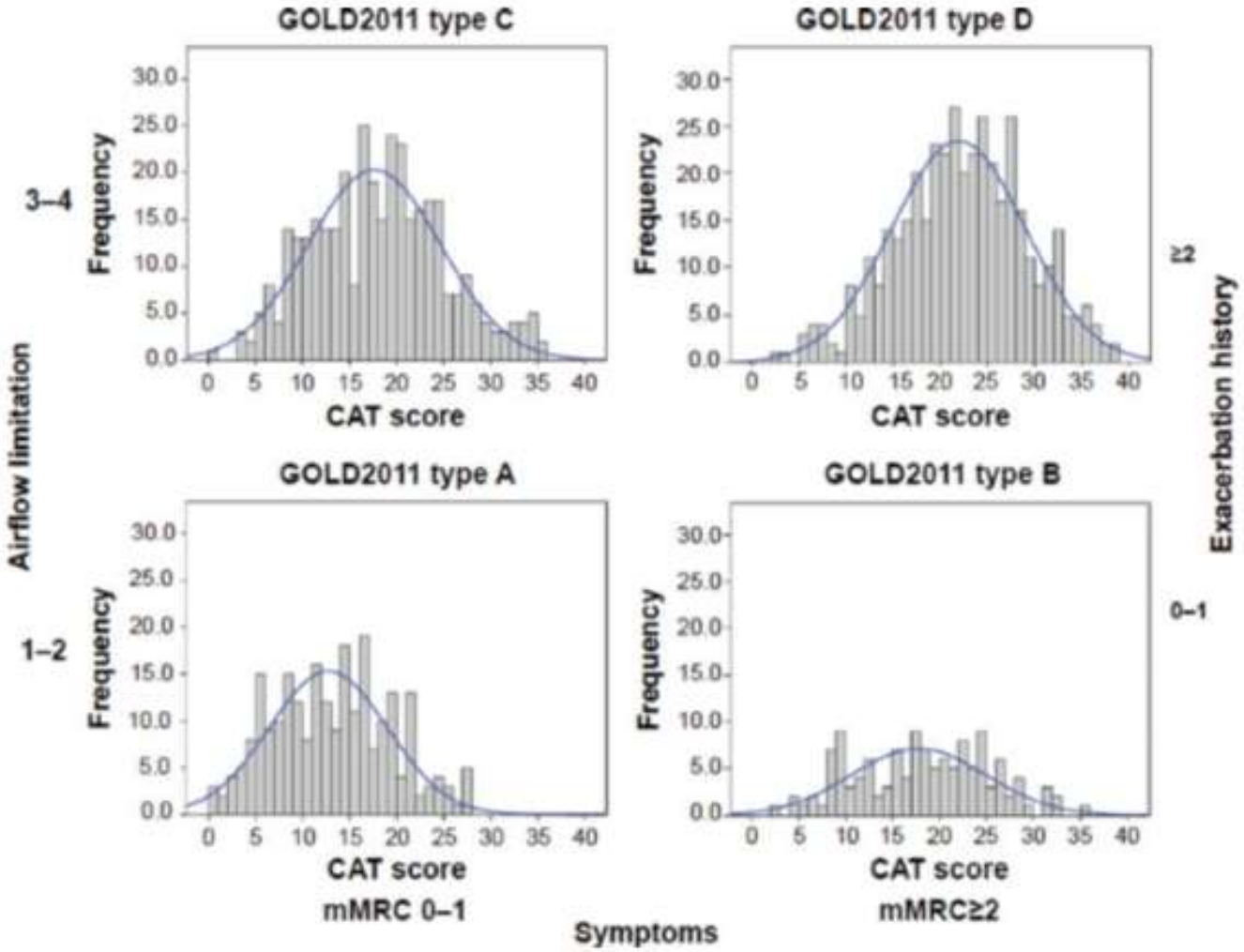
Phenotype

- Traits or characteristics
  - some of which are controlled entirely by the individual's genes whereas
  - someothers are controlled by genes but are significantly affected by environmental factors

Precision medicine ??

- Variability in clinical presentation
- Correlation between the different clinical variables at the patient level is weak
- Number of relevant clinical variables associated with outcomes
- Specific therapies for specific patient types (Mepolizumab)

Variability in clinical presentation



Cross sectional analysis of 1212 patients

Wide variability of CAT scores in all groups

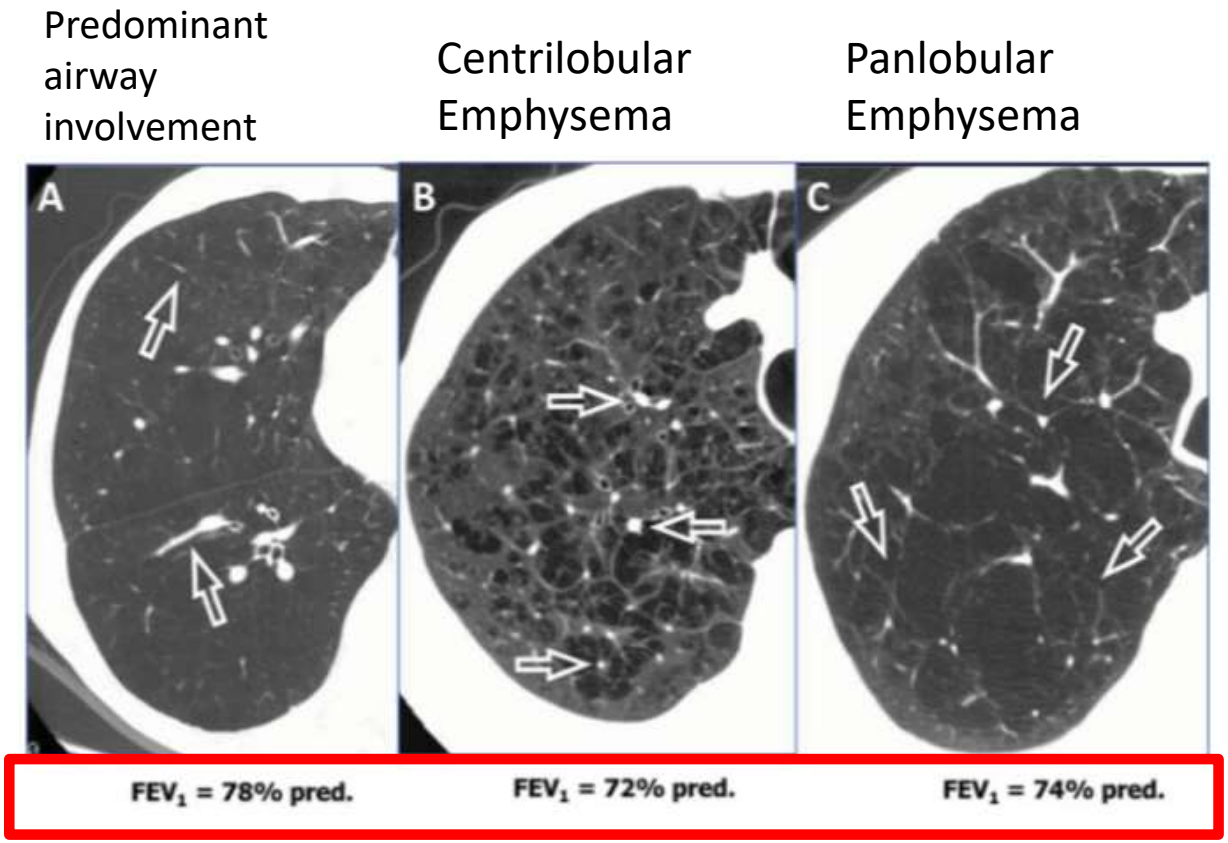
Mean values were
12.7 (6.2) for type A
18.2 (6.8) for type B
17.6 (7.0) for type C
21.8 (6.9) for type D

Lopez-Campos JL et al, Int J Chron Obstruct Pulmon Dis. 2015 May 27;10:975-84

Variability – lung function

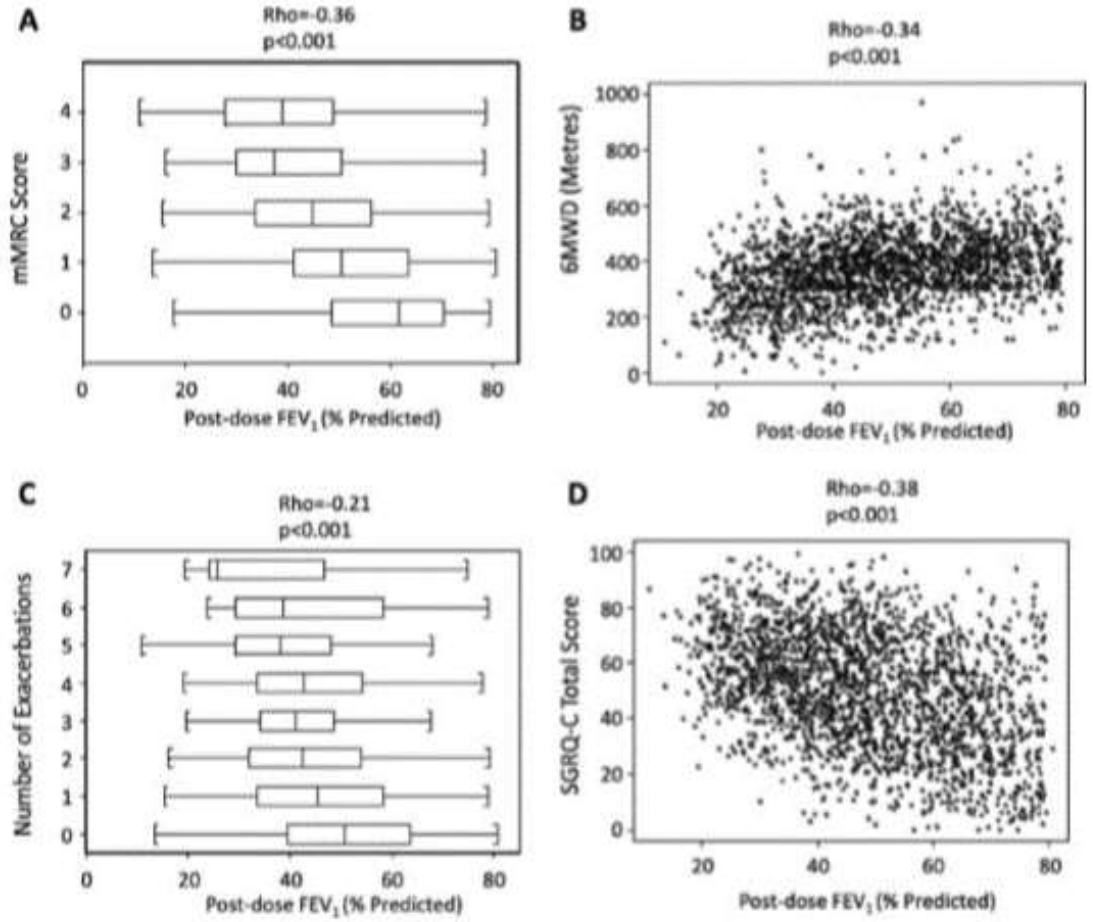
- ECLIPSE study
  - Some decline >40 ml/yr in FEV1
  - Some had improvement with treatment

Variability In Radiological Expression



Lopez-Campos JL et al, COPD. 2018 Apr;15(2):108-117

Correlation at patient level clinical variables



ECLIPSE study showed a significant correlation between FEV1 and dyspnea (mMRC) exacerbations, 6MWD QoL

But enormous dispersion of the data

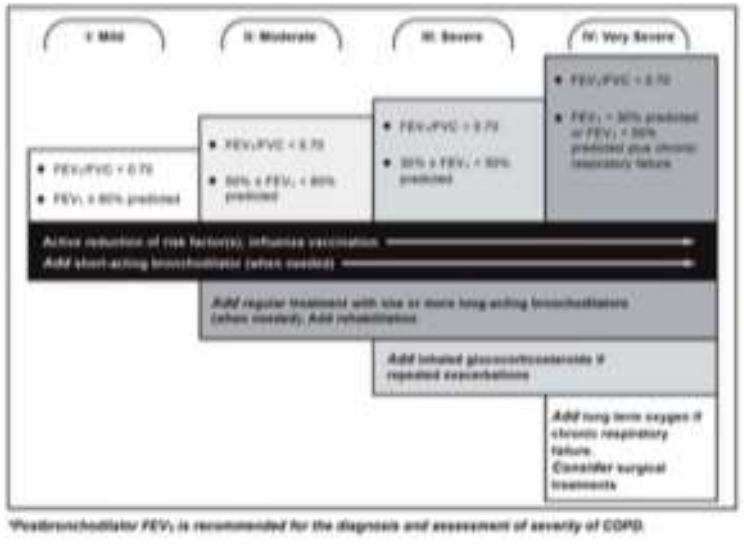
Agusti A et al, Respir Res. 2010 Sep 10;11:122

So at the patient level...

- Correlation that is clearly observed at the cohort level is *not met at the patient level*

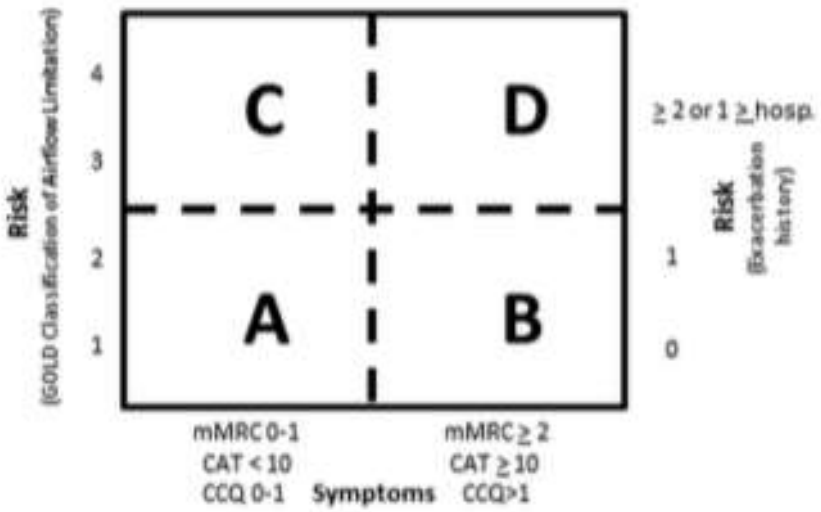
- This discrepancy between the associations found in a cohort and that found at patient level is called **ecological fallacy**

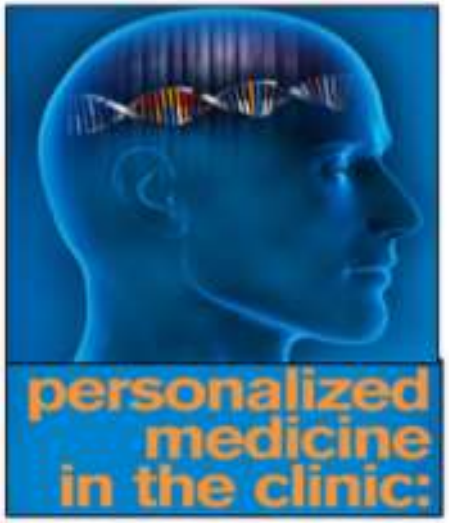
2006



Postbronchodilator FEV_1 is recommended for the diagnosis and assessment of severity of COPD.

2011





Specific therapies ??

- Biologics – mepolizumab
- LAMA/LABA/ICS
- Roflumilast
- NAC
- Antibiotics

Eosinophilic COPD Phenotype

- In review including observational and RCT's
- Eosinophilia considered >2% in blood or sputum
- 14 studies
  - Mean age 66.95 years
  - 46 pack year smoking history
  - Mean FEV1 1.62L

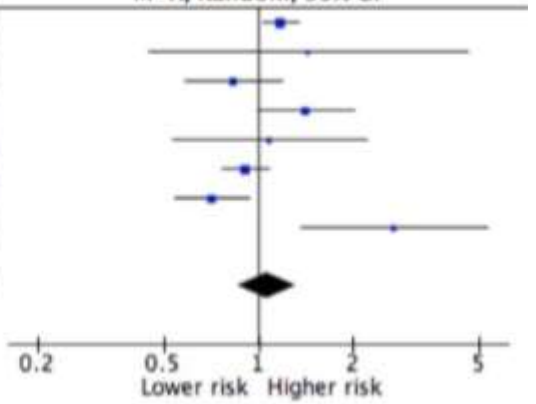
Ho J et al, Sci Rep. 2017 Oct 18;7(1):13451

Eosinophilic COPD Phenotype

- Similar risk for COPD exacerbation in 12 months
- OR 1.07, 95% CI 0.86–1.32, p = 0.55

Study or Subgroup	Eosinophilic COPD Events	Total	Non-eosinophilic COPD Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Vedel-Krogh 2015 (subgroup B)	395	1994	908	5231	20.4%	1.18 [1.03, 1.34]
Vedel-Krogh 2015 (subgroup A)	57	61	129	142	2.9%	1.44 [0.45, 4.60]
Pavord 2016 (subgroup B)	260	371	194	263	13.8%	0.83 [0.59, 1.19]
Pavord 2016 (subgroup A)	264	348	198	287	13.9%	1.41 [1.00, 2.01]
Negewo 2016	51	96	23	45	6.5%	1.08 [0.53, 2.20]
Hinds 2016	349	1777	313	1478	19.3%	0.91 [0.77, 1.08]
Duman 2015	85	504	266	1200	16.3%	0.71 [0.54, 0.93]
Couillard 2016	26	55	28	112	6.9%	2.69 [1.36, 5.31]
Total (95% CI)		**5206**		**8758**	**100.0%**	**1.07 [0.86, 1.32]**
Total events	1487		2059			

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 25.51$, df = 7 (P = 0.0006); $I^2 = 73\%$
Test for overall effect: Z = 0.60 (P = 0.55)

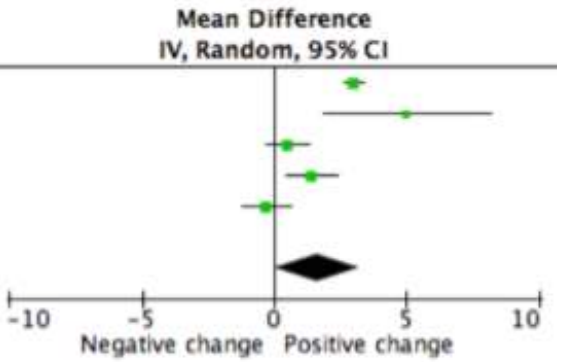


Ho J et al, Sci Rep. 2017 Oct 18;7(1):13451

Difference in FEV1

Study or Subgroup	Eosinophilic COPD Mean	SD	Total	Non-eosinophilic COPD Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bafadhel 2012 (A)	7	1	85	4	1	39	23.0%	3.00 [2.62, 3.38]
Bafadhel 2012 (B)	7	10	41	2	2	23	12.1%	5.00 [1.83, 8.17]
Pavord 2016 (subgroup A)	3.9	3.6	248	3.4	3.38	93	21.9%	0.50 [-0.32, 1.32]
Pavord 2016 (subgroup B)	3.9	5.95	266	2.5	3.25	94	21.4%	1.40 [0.43, 2.37]
Pavord 2016 (subgroup C)	3.3	3.72	269	3.6	3.85	86	21.6%	-0.30 [-1.23, 0.63]
Total (95% CI)			**909**			**335**	**100.0%**	**1.64 [0.05, 3.23]**

Heterogeneity: $Tau^2 = 2.81$; $Chi^2 = 67.08$, df = 4 ($P < 0.00001$); $I^2 = 94\%$
Test for overall effect: Z = 2.02 (P = 0.04)



Mean Difference = 1.64%, 95% CI 0.05–3.23, P < 0.001

- Bafadhel
  - Subgroup A: clinical outcomes→ 2 wks after therapy
  - Subgroup B: clinical outcomes→ 6 wks after therapy
- Pavord
  - subgroup A: fluticasone and salmeterol
  - subgroup B:fluticasone propionate
  - subgroup C:salmeterol

These subjects were → severe COPD
Baseline predicted %FEV1< 50%

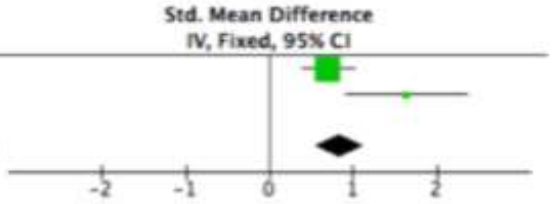
Ho J et al, Sci Rep. 2017 Oct 18;7(1):13451

Improvement in QoL

7.1 Chronic respiratory disease questionnaire

Study or Subgroup	Eosinophilic COPD Mean	SD	Total	Non-eosinophilic COPD Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Bafadhel 2012 (A)	1.01	0.64	80	0.56	0.64	86	84.2%	0.70 [0.39, 1.01]
Brightling 2005	0.35	0.3	20	-0.15	0.3	20	15.8%	1.63 [0.91, 2.36]
Total (95% CI)			**100**			**106**	**100.0%**	**0.85 [0.56, 1.14]**

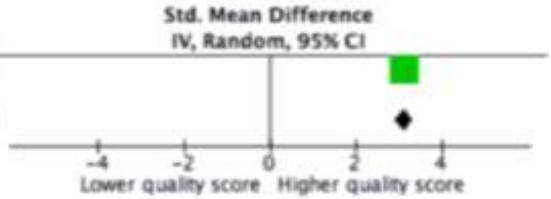
Heterogeneity: $Chi^2 = 5.36$, $df = 1$ ($P = 0.02$); $I^2 = 81\%$
Test for overall effect: $Z = 5.76$ ($P < 0.00001$)



7.2 St George's respiratory questionnaire

Study or Subgroup	Eosinophilic COPD Mean	SD	Total	Non-eosinophilic COPD Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Barnes 2016	5.59	1.105	376	0.96	1.764	376	100.0%	3.14 [2.93, 3.36]
Total (95% CI)			**376**			**376**	**100.0%**	**3.14 [2.93, 3.36]**

Heterogeneity: Not applicable
Test for overall effect: $Z = 28.78$ ($P < 0.00001$)



Ho J et al, Sci Rep. 2017 Oct 18;7(1):13451

Eosinophilic pnuemonia – Mepolizumab ??

	n	Patients	Dose	Annual rate of exacerbation	
METREX	836 (462 Eos)	GOLD D	100 mg vs placebo	Overall popl: no diff 1.49 vs 1.52 per year Eosinophilic phenotype – significant reduction 1.40 Vs 1.71 /year	RR, 0.82; 95% CI 0.68 - 0.98; *P* = .04
METREO	674	Eosinophilic pts only	100 mg 300 mg Placebo	100 mg :1.19 300 mg: 1.27 Placebo:1.49	RR:[100 mg vs placebo] 0.80; 95% CI, 0.65 - 0.98; *P* = .07; RR[300 mg vs placebo] 0.86; 95% CI, 0.70 - 1.05; *P* = .14

ID Pavord et al, N Engl J Med 2017; 377:1613-1629

Metaanalysis (presented as abstract)

- Mean annual exacerbation rate (prior year) →2.6 events/year for both groups
  - H/O ≥2 moderate/≥1 severe exacerbations in the prior year despite ICS based triple maintenance therapy
- Mepolizumab (100mg) →18% lower *mean annual rate of moderate/severe exacerbations* vs placebo
  - Rate ratio: 0.82; 95% CI: 0.71 - 0.95; **p=0.006**
- Mepolizumab 100mg Vs placebo *increased time to first moderate/severe exacerbation*
  - HR: 0.80; 95% CI: 0.68-0.94; **p=0.006**
- Mean annual rates of exacerbations requiring ED/hospitalization reduced by 15%
  - Rate ratios: 0.85; 95% CI: 0.61-1.18; p=0.328
- Severe exacerbations by 12% with mepolizumab 100mg versus placebo
  - Rate ratio: 0.88; 95% CI: 0.62-1.25; p=0.475
- **Similar results with dose of 300 mg**

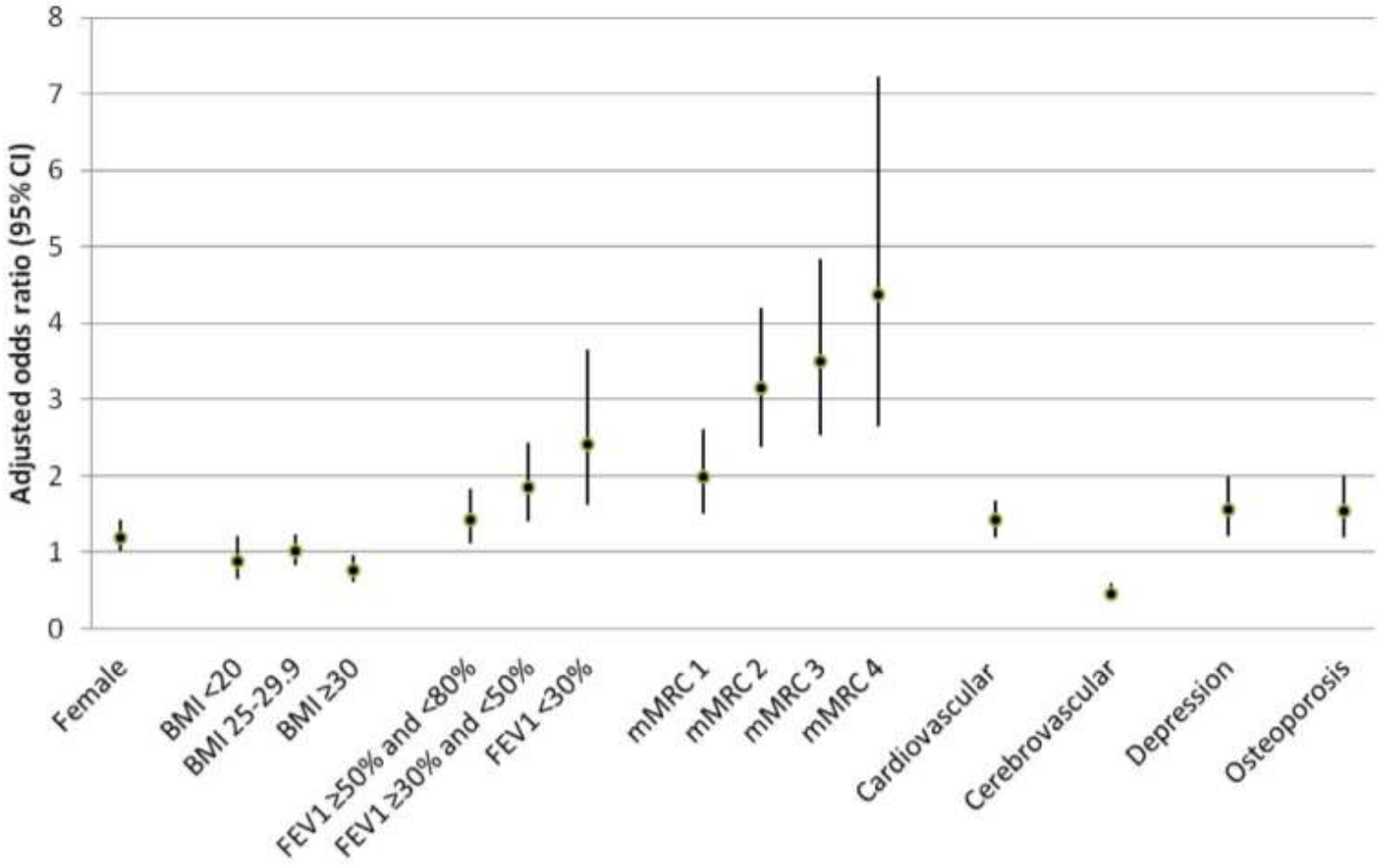
M. Bafadhel et al, Am J Respir Crit Care Med 2018;197:A5912

Frequent Exacerbator

	Type	n	Independant risk factors
McGarvey et al[1]	Population based cross sectional study	N= 9219 Frequent exacerbators = 2612 (28%)	Grade 4 mMRC FEV1 <30% Female gender Comorbid CVS
ECLIPSE[2]	3 year observational	2138	H/O previous exacerbation (OR 4.30; 95% CI 3.58 to 5.17; P<0.001) Severity of COPD H/O GERD

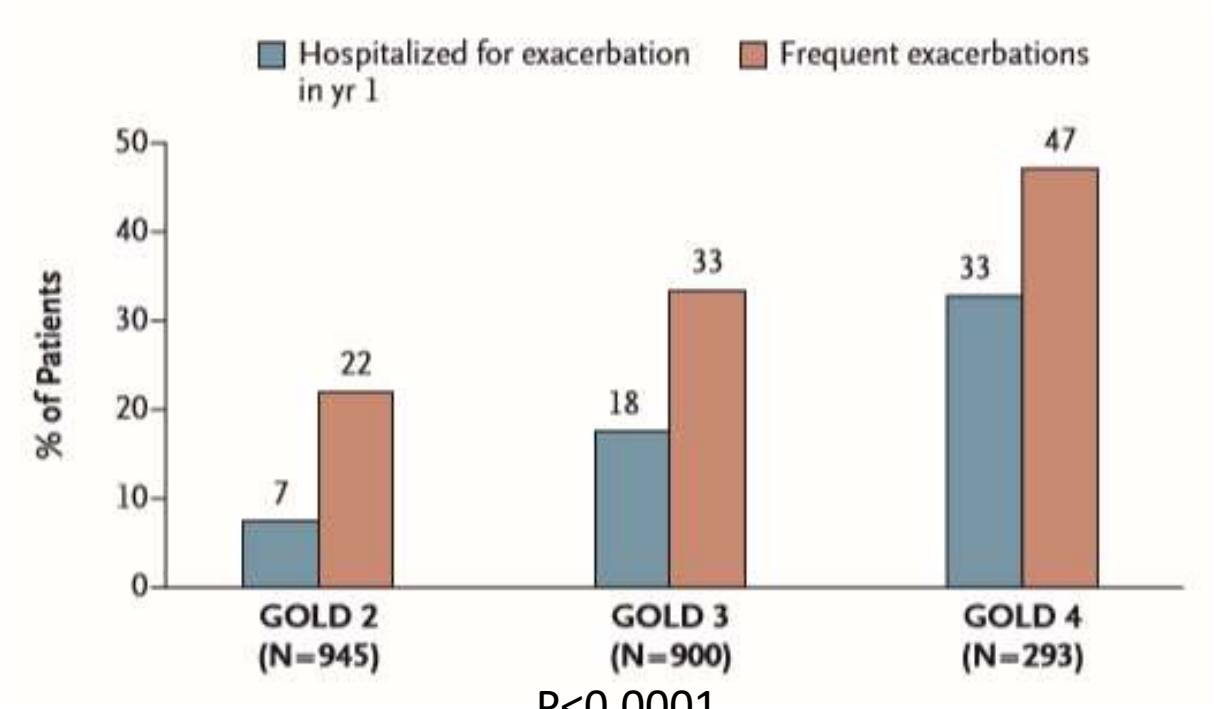
1-McGarvey L etal, Respir Med. 2015 Feb;109(2):228-37
2-Hurst JR, et al. N Engl J Med. 2010;363:1128-38.

Risk of exacerbation



1-McGarvey L et al, Respir Med. 2015 Feb;109(2):228-37

Frequent Exacerbator Phenotype



P<0.0001

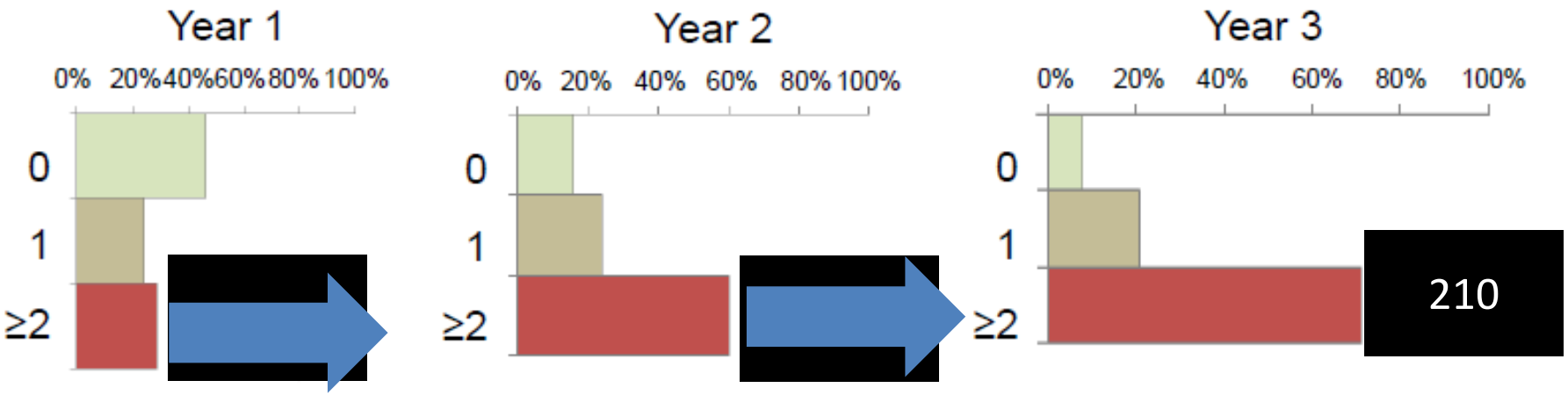
Exacerbations are more frequent and more severe with increasing COPD severity

What are the predictors of exacerbation frequency?

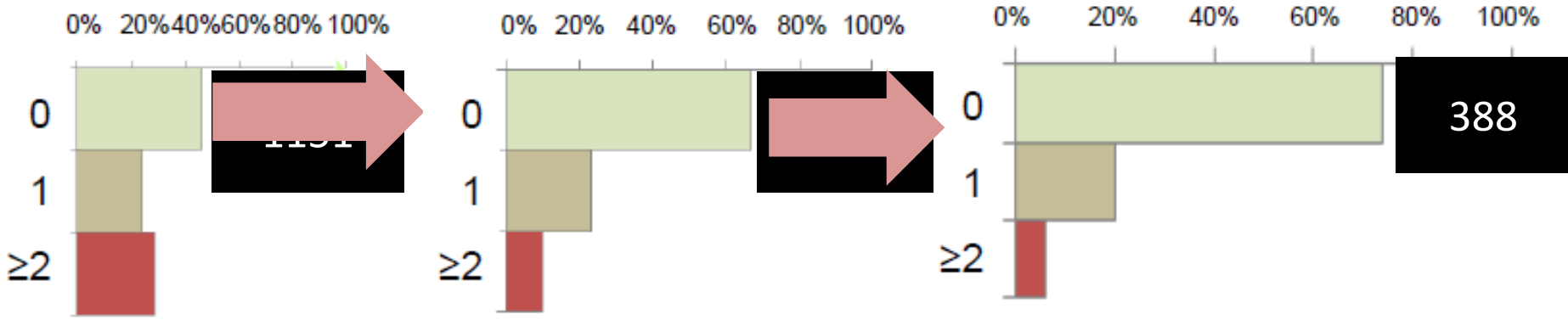
Hurst JR, et al. N Engl J Med. 2010;363:1128-38.

The 'frequent exacerbator phenotype':

ECLIPSE: Stability of the Exacerbator Phenotype



71% of Frequent Exacerbators in Year 1 and Year 2 were Frequent Exacerbators in Year 3

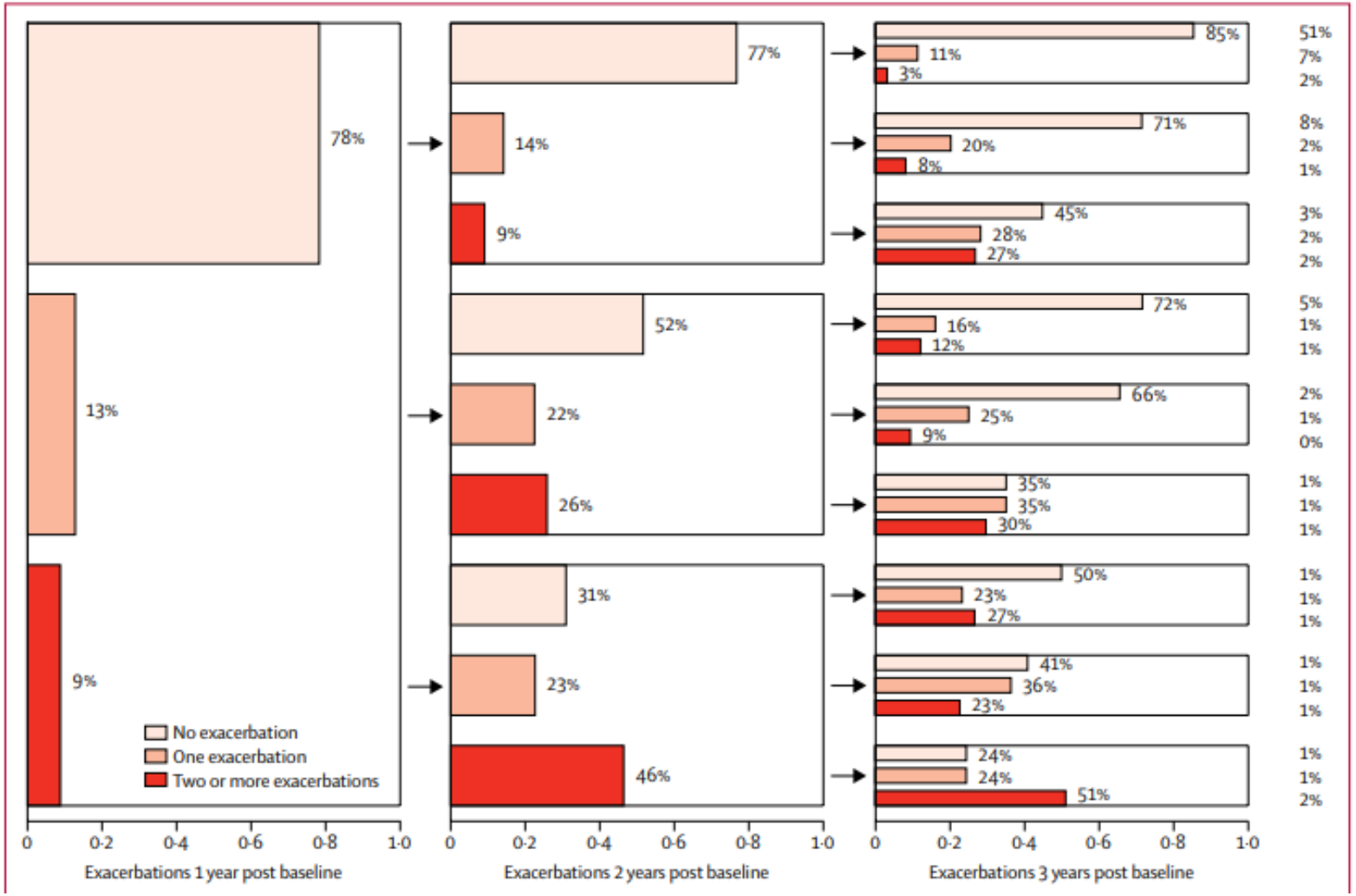


74% of patients having no exacerbations in Years 1 and Year 2 had no exacerbations in Year 3

ECLIPSE 3 year data

Hurst JR, et al. N Engl J Med. 2010;363:1128-38.

SPIROMICS – post hoc analysis



N=1105

Han MK et al, Lancet Respir Med. 2017 Aug;5(8):619-626

Ferquent exacerbator treatment ?

- LABA/LAMA/ICS
- Role of
  - NAC
  - Roflumilast
  - Antibiotics

Role of NAC

- In meta analysis of 4155 COPD patients
  - NAC-1933 patients
  - Placebo – 2222 patients

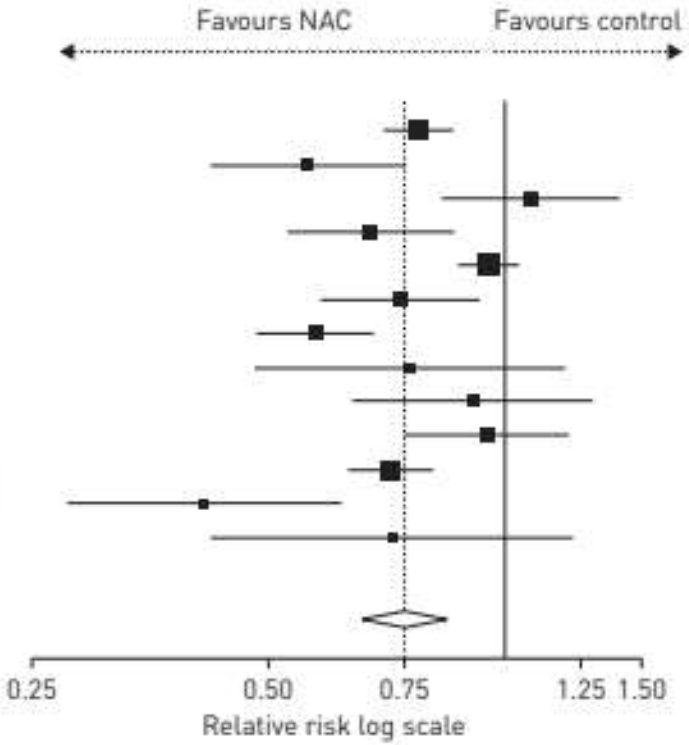
- 13 studies
  - 3 studies →high dose NAC (>600 mg/day)
  - 9 studies → low dose NAC (<600 mg/day)
  - 1 study both high and low dose

Cazzola M et al, Eur Respir Rev. 2015 Sep;24(137):451-61

Overall effect of NAC

a]

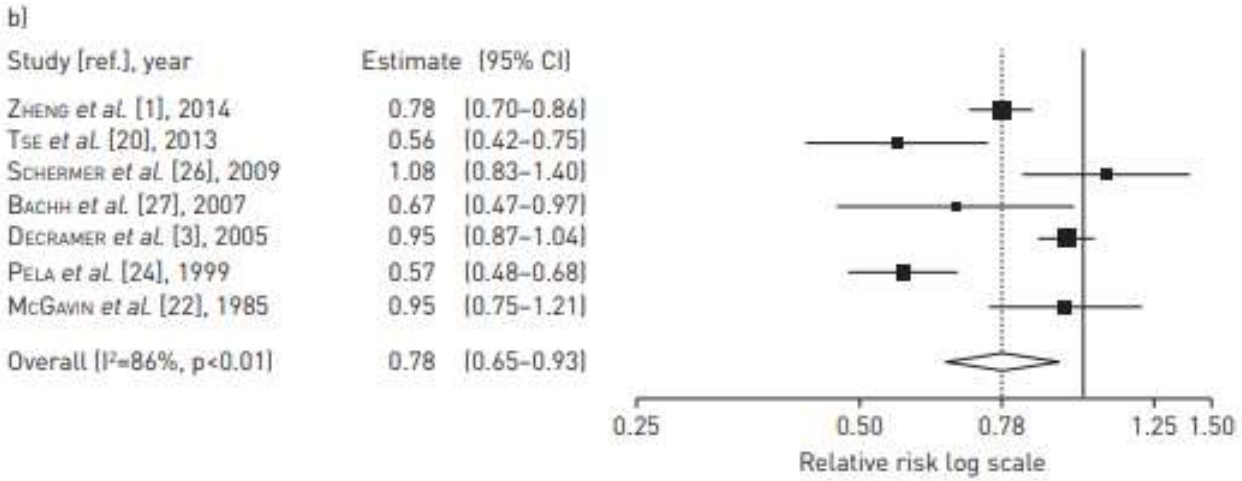
Study [ref.], year	Estimate	(95% CI)
Zheng *et al.* [1], 2014	0.78	(0.70–0.86)
Tse *et al.* [20], 2013	0.56	(0.42–0.75)
Schermer *et al.* [26], 2009	1.08	(0.83–1.40)
Bachh *et al.* [27], 2007	0.67	(0.53–0.86)
Decramer *et al.* [3], 2005	0.95	(0.87–1.04)
Gerrits *et al.* [29], 2003	0.73	(0.58–0.93)
Pela *et al.* [24], 1999	0.57	(0.48–0.68)
Hansen *et al.* [19], 1994	0.76	(0.48–1.19)
Rasmussen and Glennow [25], 1988	0.91	(0.64–1.29)
McGavin *et al.* [22], 1985	0.95	(0.75–1.21)
Boman *et al.* [23], 1983	0.71	(0.63–0.81)
Babolini *et al.* [21], 1980	0.41	(0.28–0.62)
Grassi and Morandini [28], 1976	0.72	(0.42–1.22)
Overall (I^2=80%, p<0.01)	0.75	(0.66–0.84)



NAC reduced rate of exacerbations
relative risk 0.75, 95% CI 0.66–0.84; p<0.01

Cazzola M et al, Eur Respir Rev. 2015 Sep;24(137):451-61

Overall effect – studies using spirometry

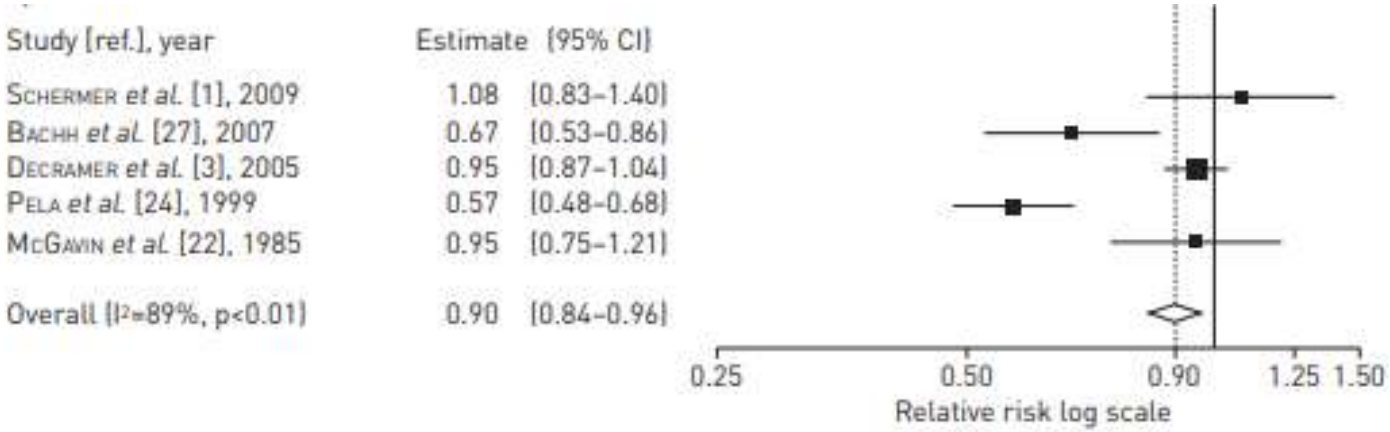


Treated n=978, placebo n=971

Relative risk 0.78, 95% CI 0.65–0.93; p<0.01

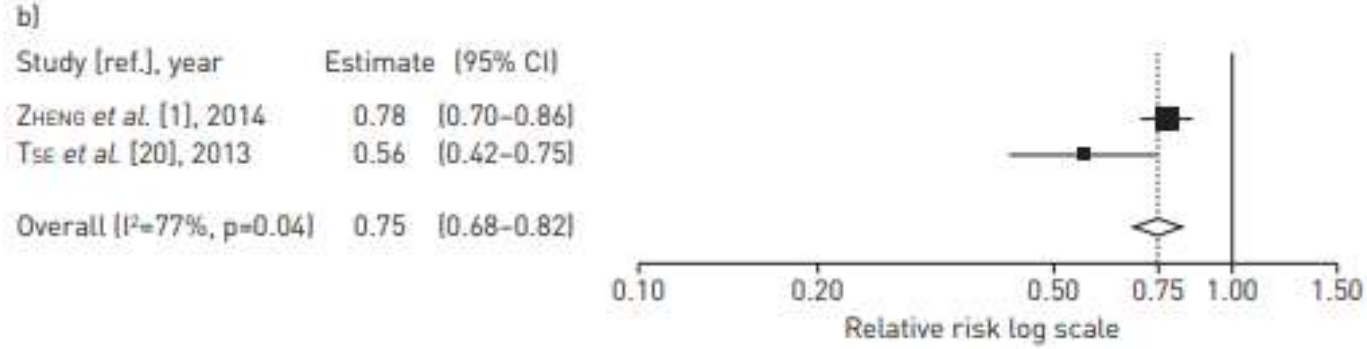
Cazzola M et al, Eur Respir Rev. 2015 Sep;24(137):451-61

NAC at low dose (<600mg/day)



5studies
n=444
placebo n=433
RR 0.90, 95% CI
0.84–0.96; p<0.01

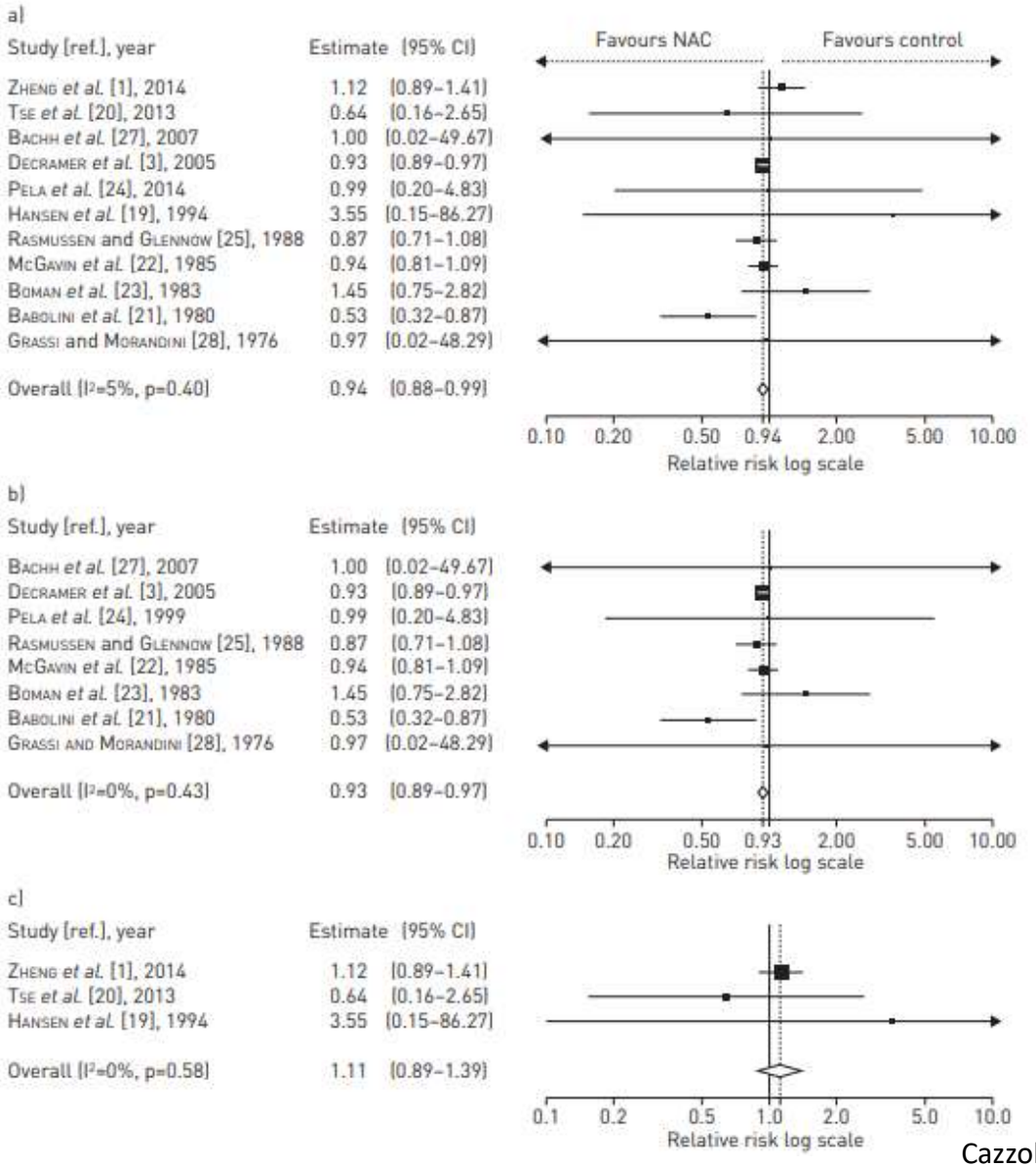
NAC at high dose (>600mg/day)



2 studies
n=534
placebo n=538
RR 0.75, 95% CI
0.68–0.82; p=0.04

Cazzola M et al, Eur Respir Rev. 2015 Sep;24(137):451-61

Adverse events



Reported in 11 RCT's

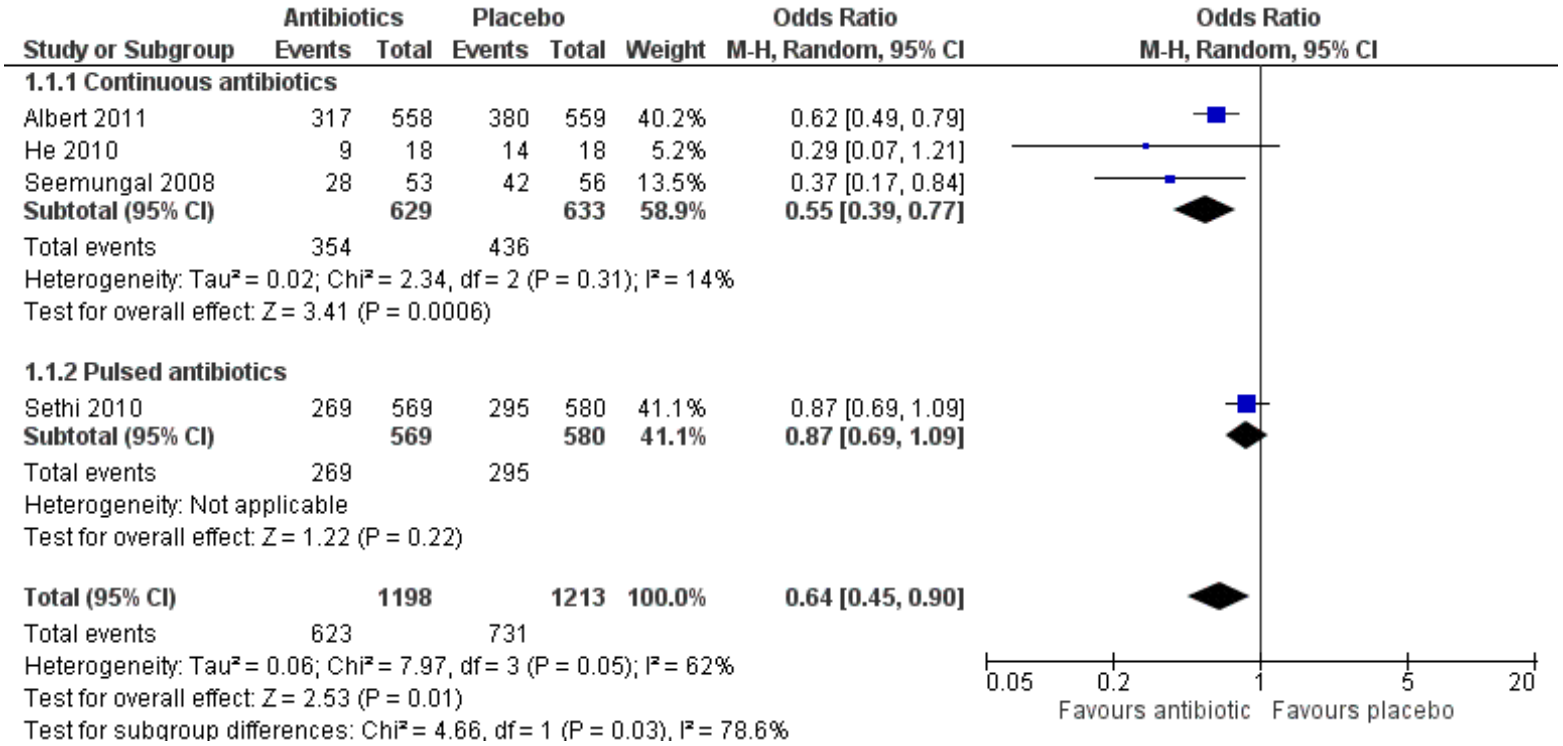
No significant difference
Not dose dependant

Cazzola M et al, Eur Respir Rev. 2015 Sep;24(137):451-61

Antibiotics ??

- Cochrane review on role of prophylactic antibiotics
- COPD on basis of spirometry
- 7 RCT's
  - 5 → continuous antibiotics (daily basis)
  - 2 → intermittent or antibiotic prophylaxis
    - 8 days every 8 weeks for 48 weeks
    - 3 days per month for 36 months

Herath SC, Poole P.Cochrane Database of Systematic Reviews 2013



Reduction in exacerbation from 69% in the control group to 54% in the treatment group (95% CI 46% to 63%)

NNT to prevent one exacerbation was 8 (95% CI 5 to 18)

Significant heterogenity

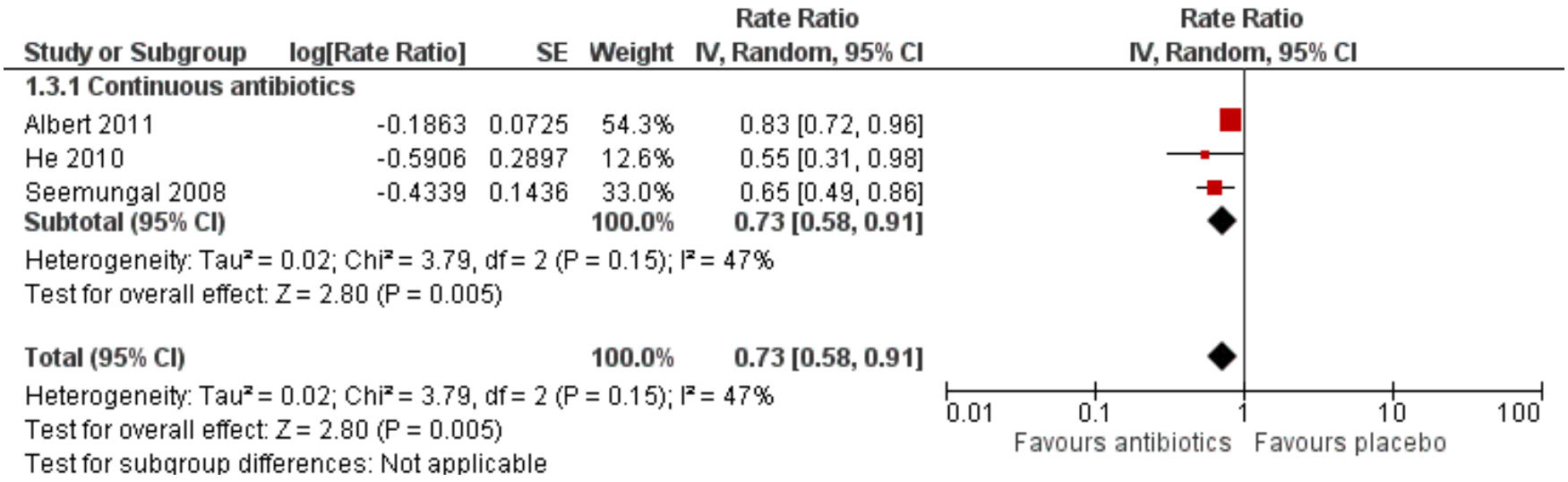
Forest plot of comparison

Antibiotics versus placebo

Number of people with ≥ 1 exacerbation

Herath SC, Poole P.Cochrane Database of Systematic Reviews 2013

Rate of exacerbation



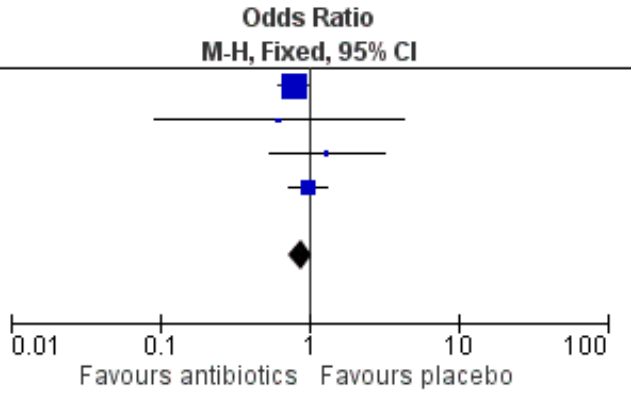
Forest plot of comparison
Antibiotics Vs placebo
Rate of exacerbation /patient/year

Herath SC, Poole P.Cochrane Database of Systematic Reviews 2013

Adverse events

Study or Subgroup	Antibiotics Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Albert 2011	184	558	212	559	60.8%	0.81 [0.63, 1.03]
He 2010	2	18	3	18	1.1%	0.63 [0.09, 4.28]
Seemungal 2008	14	53	12	56	3.7%	1.32 [0.54, 3.18]
Sethi 2010	94	569	97	580	34.4%	0.99 [0.72, 1.34]
Total (95% CI)		**1198**		**1213**	**100.0%**	**0.88 [0.73, 1.07]**
Total events	294		324			

Heterogeneity: Chi² = 1.93, df = 3 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.29 (P = 0.20)



- 2411 participants in these 4 studies
- Total of 502 adverse events reported
- Most common adverse event – GI origin
  - OR 1.58; 95% CI 1.01 to 2.47

Forest plot of comparison
Antibiotics vsplacebo, outcome
Serious adverse events

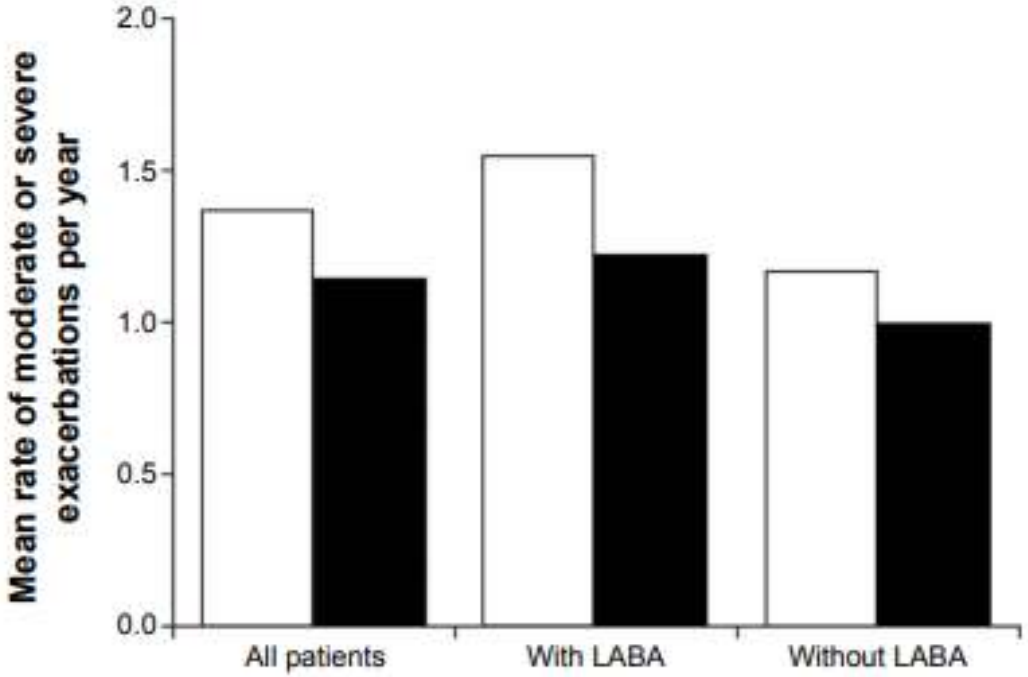
Herath SC, Poole P.Cochrane Database of Systematic Reviews 2013

Role of Roflumilast in exacerbators

Study	Type	Intervention	Result
Wedzicha JA et al[1]	Pooled data N=3091 830 – frequent exacerbators FEV1 <50% Chronic productive cough	roflumilast 500 µg OD Vs placebo	Among frequent exacerbators frequent exacerbations at 1 year 32% Vs 40.8% RR 0.799; P = 0.0148
Bateman ED et al[2]	Pooled data of 2 RCT'S FEV1 <50% Chronic productive cough	roflumilast 500 µg OD Vs placebo	Frequent exacerbators experienced a reduction in moderate or severe exacerbations RR 0.78, 95% CI 0.66-0.91; p=0.002

1-Wedzicha JA et al,Chest. 2013;143(5):1302–1311
2-Bateman ED et al, Eur Respir J. 2011 Sep;38(3):553-60

Roflumilast



	All patients	With LABA	Without LABA
□ Placebo	1.374 (n=1,554)	1.554 (n=793)	1.17 (n=761)
■ Roflumilast	1.142 (n=1,537)	1.232 (n=749)	1.999 (n=788)
Rate ratio (95% CI)	0.831 (0.75–0.92)	0.793 (0.69–0.91)	0.854 (0.74–0.99)
Two-sided *P*-value	0.0003	0.0011	0.0387

- Moderate to severe exacerbations of COPD were reduced by
  - 20.7% in patients taking roflumilast concomitantly with a LABA (P=0.001)
  - 14.6% in patients taking roflumilast alone (P=0.039)

Bateman ED et al, Eur Respir J. 2011;38(3):553–560

Adverse events – Roflumilast

Adverse reaction, % (n)	Roflumilast (n=4,438)	Placebo (n=4,192)
Diarrhea	9.5 (420)	2.7 (113)
Weight loss	7.5 (331)	2.1 (89)
Nausea	4.7 (209)	1.4 (60)
Back pain	3.2 (142)	2.2 (92)
Influenza	2.8 (124)	2.7 (112)
Insomnia	2.4 (105)	1.0 (41)
Decreased appetite	2.1 (91)	0.4 (15)

≥2% adverse rections

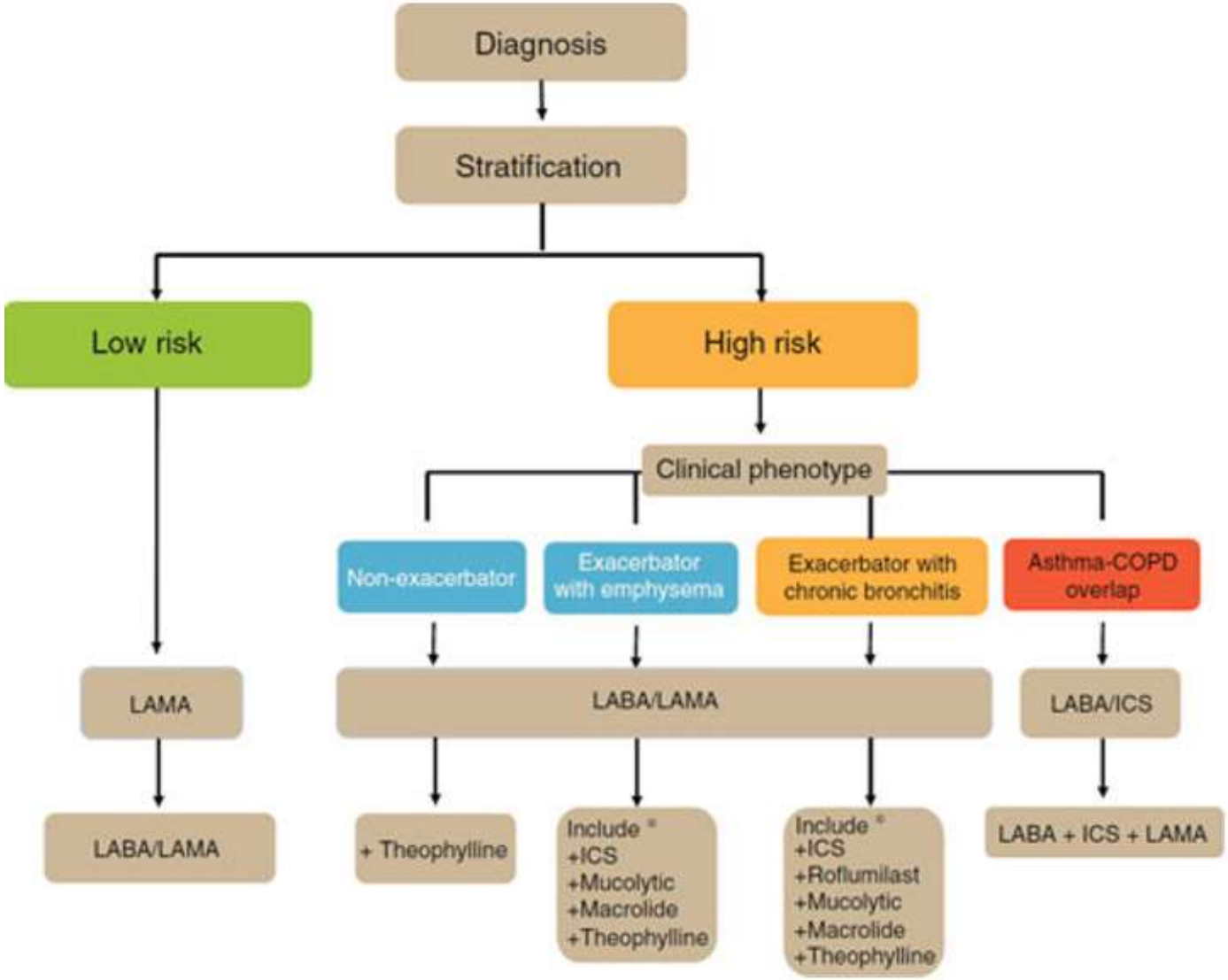
4 RCT's of 1 year

4 RCT's of 6 months

Michalski JM et al, Clin Pharmacol Ther. 2012 Jan;91(1):134-42

- With these → concept of clinical phenotypes
- Aid to treatment
- Spanish guidelines were first(2012)

Clinical phenotypes



Miravitlles M et al, Arch Bronconeumol. 2017 Jun;53(6):324-335

Risk Stratification

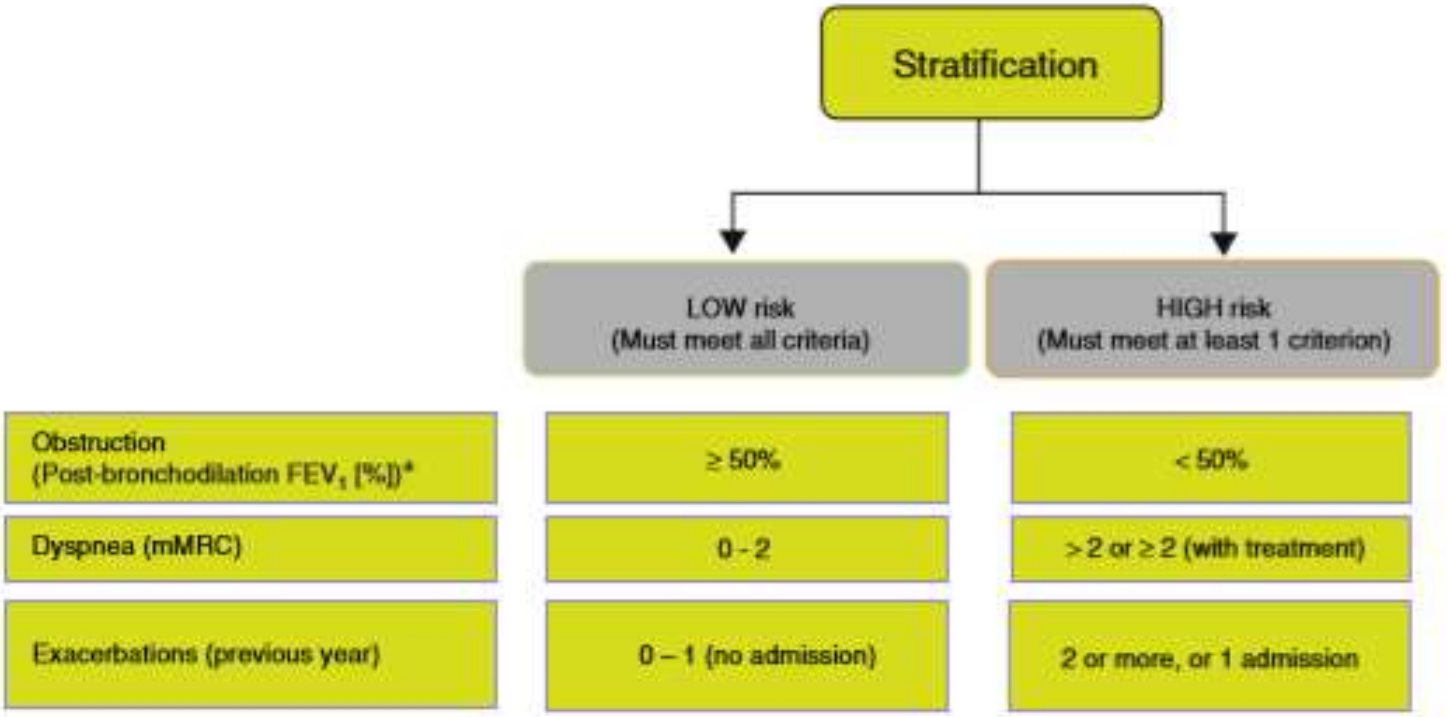


Fig. 1. Risk stratification in patients with COPD.

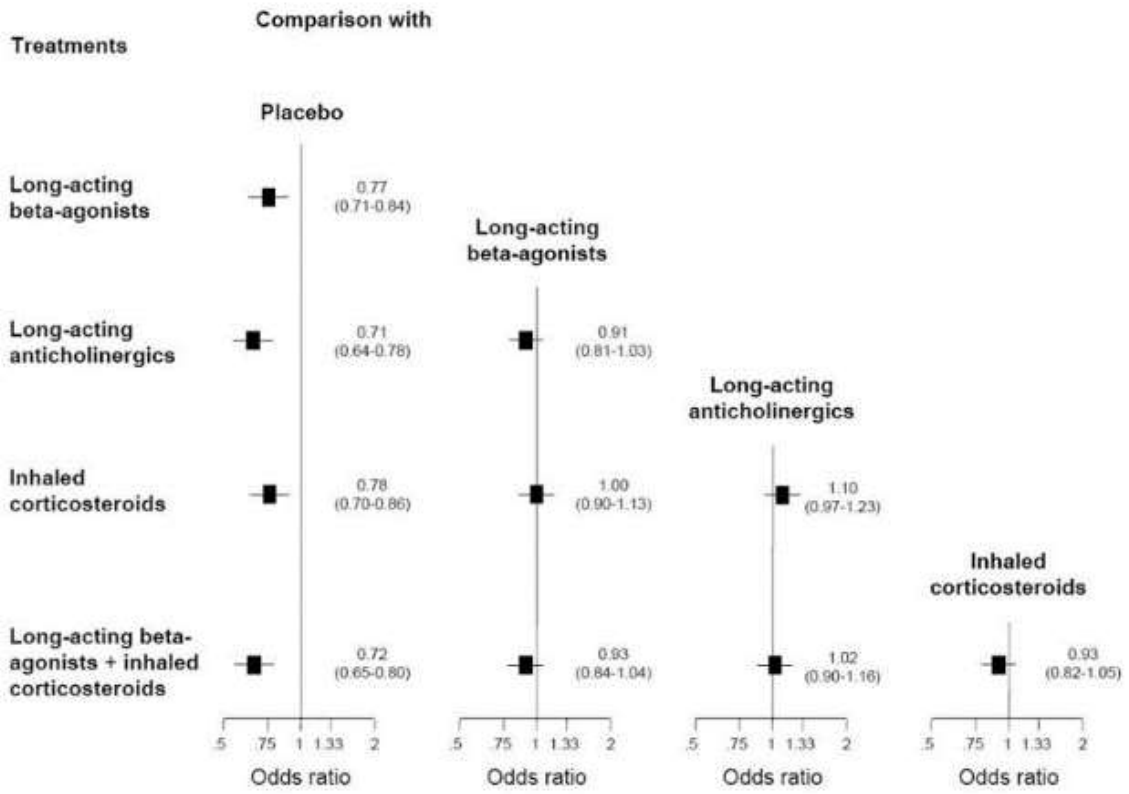
Miravitlles M et al, Arch Bronconeumol. 2017 Jun;53(6):324-335

Treatment of low risk patients

- Long acting bronchodilator
  - LAMA > LABA

- If not adequately controlled
  - Dual LABD

Inhaled Drugs To Reduce Exacerbations



35 trials, n=26,786

All were better compared to placebo

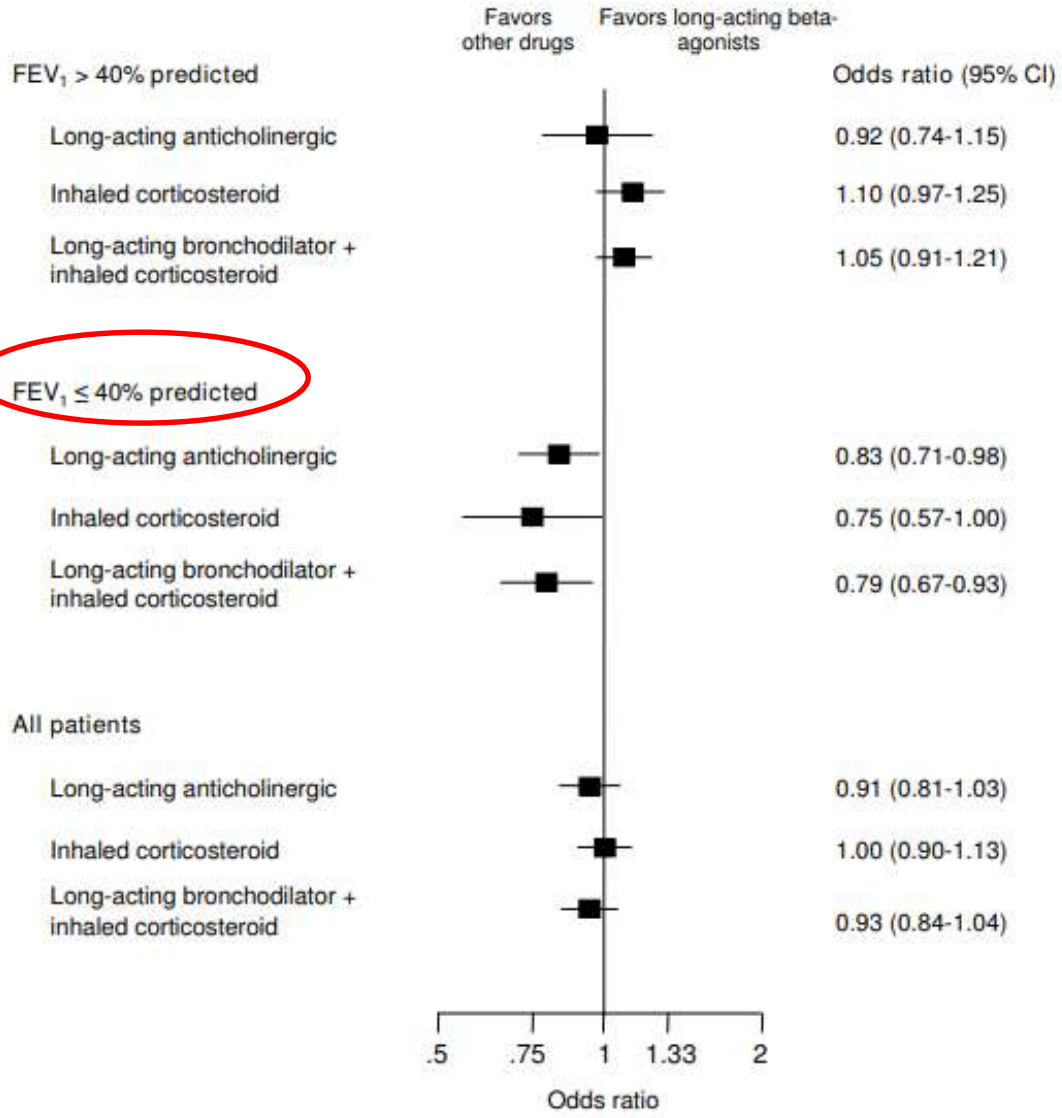
Median Age : 64 years

Median FEV1: 42%

Puhan MA et al, BMC Med. 2009 Jan 14;7:2

LAMA Vs LABA

LAMA Vs LABA



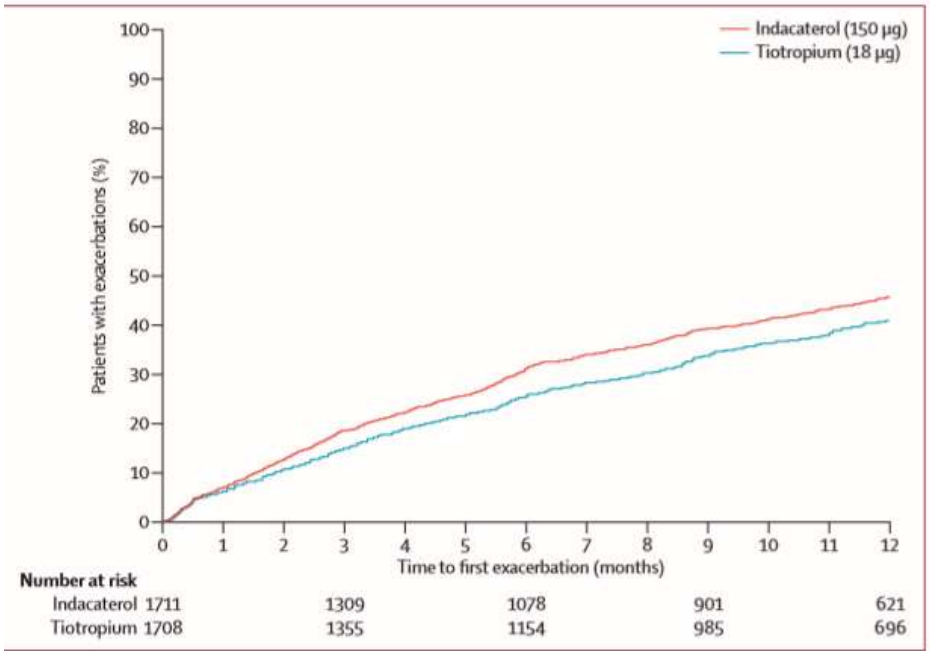
Puhan MA et al, BMC Med. 2009 Jan 14;7:2

INVIGORATE Trial

- 52 wk multicenter randomized double dummy
- 408 centers,41 countries
- 3439 enrolled patients
  - Indacaterol(150 mcg OD) Vs Tiotropium(18 mcg OD)
  - Post BD FEV1 between 30% - 50%
  - ≥ 1 moderate or severe exacerbations in the previous 12 months
  - Excluded patients with h/s/o asthma

Decramer ML et al, Lancet Respir Med. 2013 Sep;1(7):524-33

INVIGORATE Trial



- Annualised rate of exacerbations
  - higher with indacaterol than tiotropium
  - 0·90 vs 0·73; rate ratio 1·24; 95% CI 1·12 to 1·37; p<0·0001

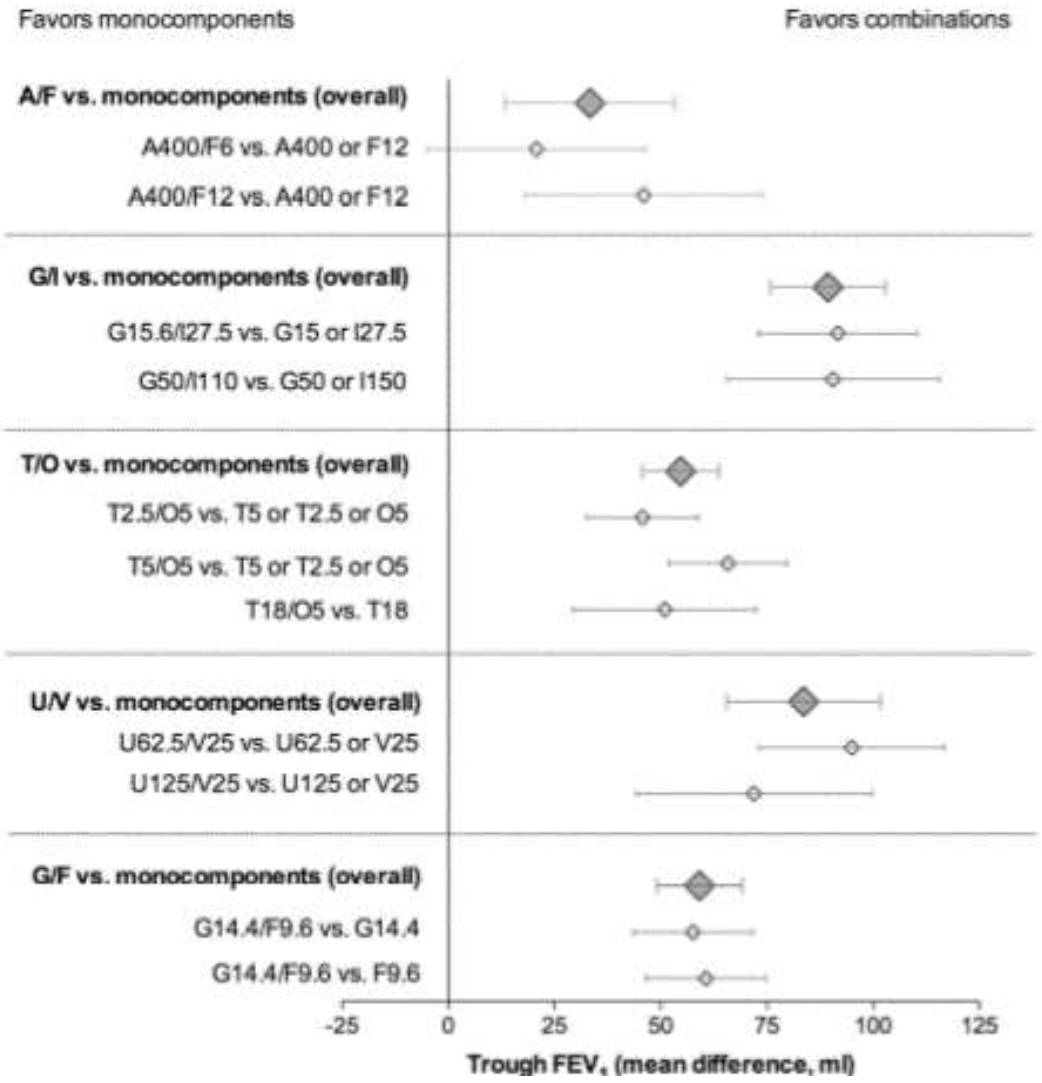
Decramer ML et al, Lancet Respir Med. 2013 Sep;1(7):524-33

Dual Vs single bronchodilation

- In meta analysis
- 22 RCT's
- Period of treatment ranged from 12 to 52 weeks
- 23,168 COPD patients
  - combinations, n = 10,328
  - monocomponents, n = 12,840

Calzetta L et al, Chest. 2016 May;149(5):1181-96

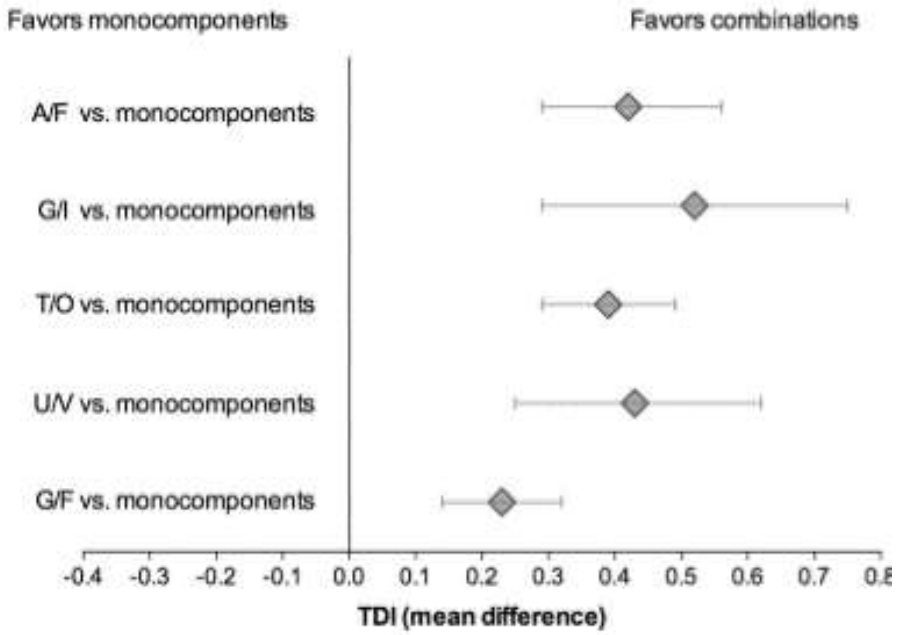
Dual Vs single bronchodilation

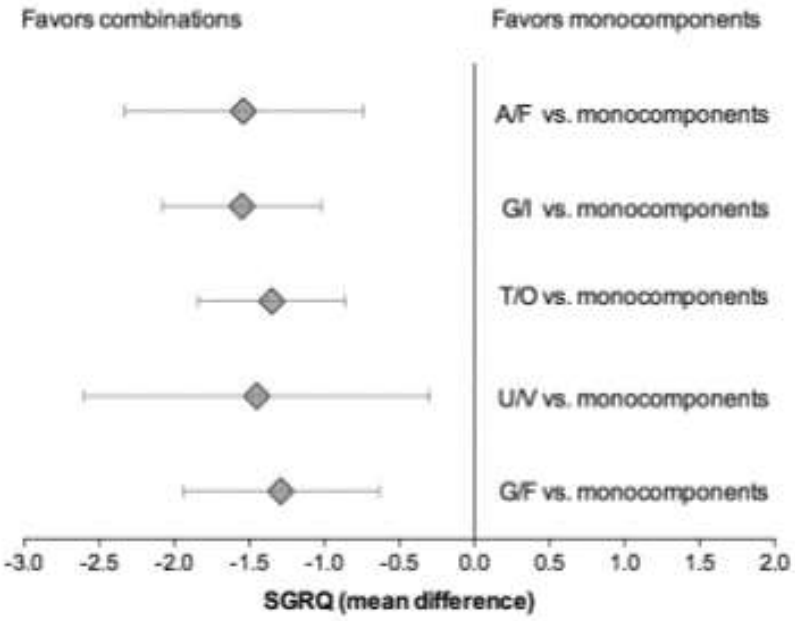


FEV1 improved 35 ml to 95 ml with different combinations

Calzetta L et al, Chest. 2016 May;149(5):1181-96

Symptomatic improvement ??





Not significant clinically !!!
Adverse events : no differnce

Calzetta L et al, Chest. 2016 May;149(5):1181-96

Indaceterol/Glycopyrrinium Vs Salemeterol/Fluticasone

Study	Type	Popln included	Mean FEV1	Result
ILLUMINATE[1]	Multicenter RCT N = 523 26 Wks	Post BD FEV1 40-80 % No exacerbations No h/o asthma	60.2 %	Significantly improved FEV1,TDI score, rescue medication usage
LANTERN[2]	Multicenter RCT N = 744 26 Wks	Post BD FEV1 30-80 % mMCR≥2 1 exacerbation (21%) No h/o asthma	51.8 %	Reduced exacerbations, RR 0.43 (95% CI 0.25-0.76;p)
FLAME [3]	Multicenter RCT N = 3332 52 Wks	Post BD FEV1 25-60 % mMCR≥2 ≥1 exacerbation No h/o asthma	44.1 %	Reduced exacerbations RR, 0.89; 95% CI, 0.83 to 0.96; P=0.003 Redued mod/sev exacerbation and time to 1st exacebation

1- Vogelmeier CF et al, Lancet Respir Med. 2013 Mar;1(1):51-60
2- Zhong N et al, Int J Chron Obstruct Pulmon Dis. 2015 Jun 5;10:1015-26
3- Wedzicha JA et al, N Engl J Med. 2016 Jun 9;374(23):2222-34

Role of ICS

	FEV1 (%)	Exacerbations	n	Comparator	Withdrawal	Outcome
SUNSET[1]	≥40 - <80%	1	1053	I/G Vs T/S/F	Abrupt	Small decrease in lung function No difference in COPD exacerbations eosinophils ≥ 300 cells/µL Difference in exacerbations Most likely benefit from continuation of triple therapy
WISDOM[2]	< 50	1	2485	T/S/F Vs T/S	Stepwise reduction (6 wks)	Non inferiority to 1st mod/sev exacerbation
COSMIC[3]	30 - 70	≥2	373	S/F Vs S	Abrupt	Greater decline in FEV1
INSTEAD[4]	50-80	0	581	S/F Vs I	Abrupt	Non inferiority in trough FEV1 after 12 wks

T-Tiotropium
S-Salmeterol
F-Fluticasone
I- Indacaterol
G- Glycopyrrinium

1- Chapman KR et al, Am J Respir Crit Care Med. 2018 Aug 1;198(3):329-339
2- Magnussen H et al, N Engl J Med. 2014 Oct 2;371(14):1285-94
3- Wouters EF et al, Thorax. 2005 Jun;60(6):480-7
4- Rossi A et al, Eur Respir J. 2014 Dec;44(6):1548-56

ACOS

- Coexistence of increased variability of airflow and incompletely reversible airway obstruction

- Prevalence → 12-55% in COPD patients

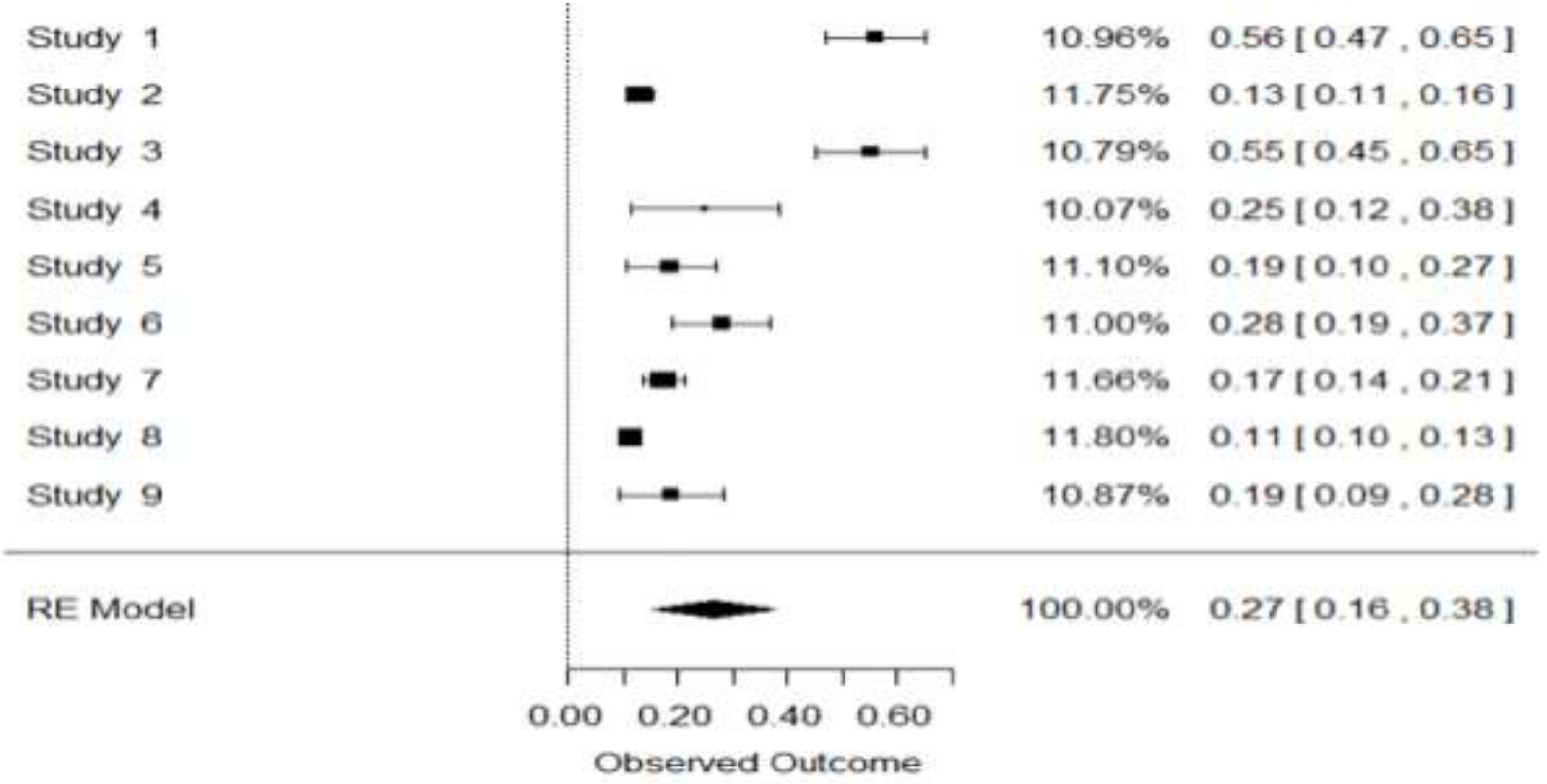
Alshabanat A et al, PLoS One. 2015 Sep 3;10(9):e0136065

Prevalence of ACOS

- In review of 13 studies
  - Overlap phenotype as any COPD patient with atleast ≥1 of the following findings:
    - Physician diagnosed asthma or self reported physician diagnosis of asthma
    - Reversibility testing (>12%and atleast 200ml change in FEV1 from baseline)
    - Peak Expiratory Flow variability (>20% change)
    - Airway hyperresponsiveness to methacholine or histamine

Alshabanat A et al, PLoS One. 2015 Sep 3;10(9):e0136065

ACOS - Prevalence



Pooled prevalence of overlap was 27% (95% CI:0.16–0.38, p<0.0001

Alshabanat A et al, PLoS One. 2015 Sep 3;10(9):e0136065

ACOS

- 2012 consensus (GINA & GOLD) guideline
  - 2 major or 1 major and 2 minor
  - Major criteria
    - Previous h/o of asthma or
    - BDR to albuterol >15% or 400ml
  - Minor criteria
    - Blood eosinophils > 5%
    - IgE > 100 IU
    - Two separate BDR to albuterol > 12% and 200ml

ACOS – how do they progress?

- 8832 participants
- Population based observational study
- Grouped into 6 categories
  - 2199 never smokers
  - 5435 ever smokers
  - 158 with asthma
  - 320 with COPD
  - 68 with asthma COPD overlap with early onset asthma
  - 202 with asthma COPD overlap with late onset asthma
- Followed for 22years

Lange P et al, Lancet Respir Med. 2016 Jun;4(6):454-62

	Never-smokers (n=1980)	Ever-smokers (n=4831)	Asthma (n=124)	COPD (n=303)	ACO with early asthma onset (n=62)	ACO with late asthma onset (n=188)
Male sex	590 (30%)	2237 (46%)	32 (26%)	199 (66%)	27 (44%)	100 (53%)
At first examination						
Age (years)	45 (13)	46 (11)	43 (13)	51 (8)	46 (10)	53 (8)
FEV_1						
Mean (L)	3·00 (0·96)	3·06 (0·88)	2·87 (0·91)	2·61 (0·70)	2·13 (0·81)	2·10 (0·79)
% of predicted value	92 (16)	90 (15)	87 (16)	77 (14)	63 (18)	67 (20)
FEV_1 to FVC ratio (%)	83 (8)	82 (8)	81 (9)	74 (10)	68 (12)	70 (12)
Current smokers	..	3514/4821 (73%)	35/124 (28%)	285/303 (94%)	38/62 (61%)	161/187 (86%)
Smoking history (pack-years)	..	14 (16)	3 (3)	30 (15)	14 (13)	18 (12)
First available FEV_1 in participants younger than 40 years of age at enrolment						
Mean (L)	3·64 (0·95)	3·53 (0·89)	3·40 (0·81)	3·01 (0·81)	2·77 (0·95)	2·87 (0·97)
% of predicted value	93 (15)	91 (15)	87 (13)	78 (13)	71 (17)	76 (21)
FEV_1 >80% of predicted	626/752 (83%)	1303/1657 (79%)	43/56 (77%)	15/30 (50%)	4/14 (29%)	8/16 (50%)
At final examination						
Age (years)	64 (14)	64 (12)	61 (15)	69 (8)	63 (11)	70 (8)
Mean duration of follow-up	19 (8–27)	19 (8–27)	18 (8–27)	18 (8–27)	17 (9–26)	17 (9–26)
FEV_1						
Mean (L)	2·58 (0·91)	2·55 (0·83)	2·40 (0·92)	1·77 (0·65)	1·60 (0·77)	1·24 (0·56)
% of predicted value	99 (18)	93 (18)	88 (19)	65 (20)	57 (21)	51 (20)
FEV_1 to FVC ratio (%)	79 (6)	77 (7)	77 (7)	60 (8)	58 (9)	54 (11)
Current smokers	6/1950 (<1%)	2560/4796 (53%)	23/124 (19%)	230/302 (76%)	29/62 (47%)	103/186 (55%)
Smoking history (pack-years)	0 (1)	28 (24)	3 (5)	46 (22)	23 (21)	34 (21)
Medication for airway disease	51/1951 (3%)	163/4785 (3%)	63/124 (51%)	35/298 (12%)	52/61 (85%)	166/188 (88%)
Decline in FEV_1 (mL per year)	24 (31)	28 (30)	26 (29)	46 (28)	31 (37)	51 (38)

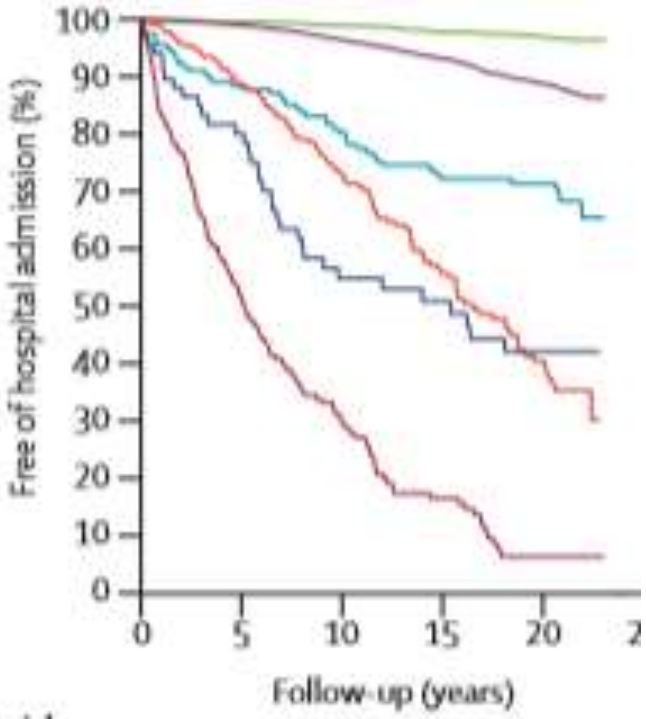
Lange P et al, Lancet Respir Med. 2016 Jun;4(6):454-62

Decline in FEV1

	Decline in FEV_1 in mL per year	p value	p value	p value	p value
Healthy never-smokers	20·9 (1·2)	Reference	0·15	<0·0001	0·19
Ever-smokers without asthma or COPD	20·7 (1·4)	0·88	0·13	<0·0001	0·17
Asthma	25·6 (3·3)	0·15	Reference	0·0003	0·77
COPD	39·5 (2·5)	<0·0001	0·0003	Reference	0·02
ACO with early asthma onset	27·3 (5·0)	0·19	0·77	0·02	Reference
ACO with late asthma onset	49·6 (3·0)	<0·0001	<0·0001	0·003	0·0001

Lange P et al, Lancet Respir Med. 2016 Jun;4(6):454-62

ACOS – hospital admission



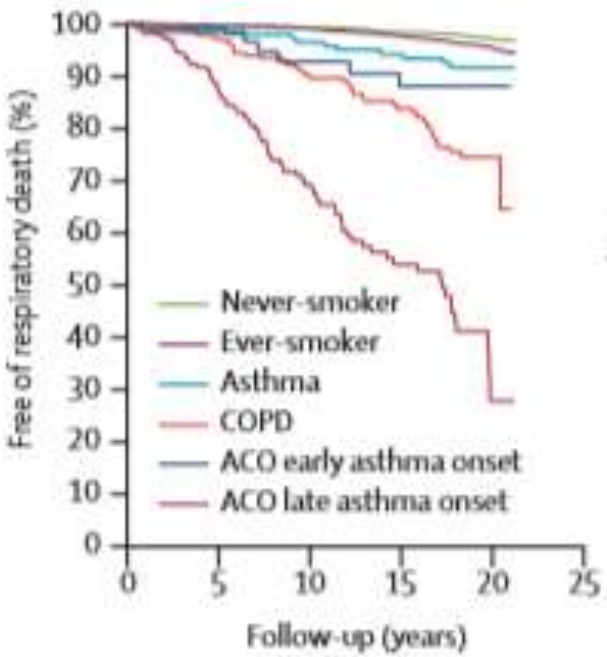
Number at risk					
Never-smoker	2199	2066	1901	1647	1402
Ever-smoker	5435	4930	4265	3566	2822
Asthma	158	134	114	91	85
COPD	320	237	144	80	40
ACO early asthma onset	68	49	31	23	18
ACO late asthma onset	202	91	38	18	5

ACO early asthma onset: HR 32·09 (95% CI 21·11–48·77); p<0·0001

ACO late asthma onset: HR 108·99 (95% CI 80·70–147·20); p<0·0001

Lange P et al, Lancet Respir Med. 2016 Jun;4(6):454-62

ACOS – mortality



ACO early asthma onset: HR 5·32 (95% CI 2·27–12·44); p=0·0001

ACO late asthma onset: HR 44·34 (95% CI 30·63–64·18); p<0·0001

Lange P et al, Lancet Respir Med. 2016 Jun;4(6):454-62

ACOS-response to treatment ?

- Largely extrapolated
- Few small studies

	Type	n	Response
Lim Hs et al	Retrospective observational	ACOS 125 90 ICS 35 non ICS	FEV1 decrease 9.61 mL/year Vs 15.68ml/yr P 0.598 Risk of exacerbation No decrease RR1.24, 95% CI 0.44-3.46
Jia Xi Feng et al	Prospective	ACOS 127 Control 131 ACOS – 2 mg budesonide TDS X 6 months	Improved spirometry and measures of hyperinflation, sputum eosinophils, serum IgE, and FeNO after treatment
Lee SY et al	Prospective	152 pts 45 ACOS 3 mnths ICS/LABA after 3 week washout period	FEV1 better in ACOS 240.2±33.5 vs 124.6±19.8 mL, P=0.002 Better in mild to moderate airflow limitation

1-Lim HS et al, Ann Allergy Asthma Immunol. 2014 Dec;113(6):652-7
2- Jia-Xi Feng et al, J Korean Med Sci. 2017 Mar; 32(3): 439–447
3- Lee SY et al, Int J Chron Obstruct Pulmon Dis. 2016 Nov 8;11:2797-2803

Different phenotypes – different demographic and clinical characters

- The inclusion criteria were patients
  - Age > 40 years
  - Smokers or exsmokers (of at least 10 pack-years)
  - COPD diagnosed on the basis of spirometric tests performed at inclusion or a maximum of 12 months earlier with a
    - post BDR FEV1/FVC 0.7
  - The exclusion criteria
    - presence of other severe chronic respiratory diseases (cystic fibrosis, pulmonary fibrosis, active neoplasm)
    - inability to read or understand the questionnaires used in the study

Population based studies - phenotyping

	Miravitlles et al[1] (n=3125)	Rubio MC et al[2] (647)	CHAIN cohort[3] (n=831)
NE(%)	61	47.5	66.2
ECB(%)	19	29	11.9
EE(%)	4	17	4.6
ACOS(%)	16	6.5	15

All 3 studies were done in Spanish population

1- Miravitlles M et al, Int J Tuberc Lung Dis. 2015 Aug;19(8):992-8
2- Rubio MC et al, Int J Chron Obstruct Pulmon Dis. 2017; 12: 2373–2383
3- Cosio BG et al, PLoS One. 2016 Sep 29;11(9):e0160770

Demographic And Clinical Characters

	0	NE	ACOS	FEE	FECB	p
	19 (2.3%)	550 (66.2%)	125 (15.0%)	38 (4.6%)	99 (11.9%)	
Female, n (%)	2 (10.5)	90 (16.4)	23 (18.4)	12 (31.6)	14 (14.1)	0.126
Age, mean ± SD	69.0±9.4	67.4±9.1	66.5±8.7	68.4±8.7	69.5±8.1	0.113
Pack-year, mean ± DE	50.8±28.4	56.3±28.7	53.2±26.2	52.9±26.3	60.8±30.0	0.270
Current smoker, n (%)	2 (10.5)	156 (28.4)	44 (35.2)	10(26.3)	28 (28.3)	0.218
BMI, mean ± SD	28.7±4.8	28.0±5.7	29.0±5.5	28.0±4.8	27.8±4.8	0.367
Symptoms, n (%)						
-cough and sputum	0 (0.0)	315 (57.3)	75 (60.0)	0 (0.0)	99 (100.0)	<0.001
-dyspnea (mMRC >2)	10 (52.6)	233 (42.4)	56 (44.8)	16 (43.2)	67 (67.7)	<0.001
CAT (m ± SD)	11.28±7	11.74±7	12.02±7,5	11.61±6,1	17.14±8,2	<0.001
FEV_1%, m ± SD	58.2±19.8	60.7±21.1	61.2±18.1	55.3±15.7	52.9±19.4	0.004
FVC%, m ± SD	83.3±21.4	86.7±23.3	84.9±18.5	86.3±24.7	80.1±23.1	0.116
FEV_1/FVC, m ± SD	53.1±12.6	52.9±11.5	54.8±10.9	49.1±9.9	49.2±10.9	0.001
Prevalence of GOLD airflow limitation, n (%)						0.074
GOLD I	2 (10.5)	104 (19.0)	21 (16.8)	3 (7.9)	11 (11.0)	
GOLD II	11 (57.9)	263 (48.0)	69 (55.2)	21 (55.3)	39 (39.4)	
GOLD III	4 (21.1)	120 (21.9)	25 (20.0)	10 (26.3)	29 (29.3)	
GOLD IV	2 (10.5)	61 (11.1)	10 (8.0)	4 (10.5)	20 (20.2)	

Cosio BG et al, PLoS One. 2016 Sep 29;11(9):e0160770

Demographic And Clinical Characters

Variables	Total (n = 3125) mean ± SD	ACOS patients (n = 496) mean ± SD	Non-exacerbators (n = 1894) mean ± SD	Exacerbators with chronic bronchitis (n = 602) mean ± SD	Exacerbators without chronic bronchitis (n = 133) mean ± SD
Male sex, n (%)	2575 (82.4)	346 (69.8)	1617 (85.4)	514 (85.4)	98 (73.7)
Age, years	66.9 ± 9.7	64.6 ± 9.4	66.6 ± 9.7	69.3 ± 9.2	68.8 ± 9.8
BMI, kg/m^2	27.8 ± 4.3	28.3 ± 4.2	27.7 ± 4.2	27.9 ± 4.5	26.5 ± 4.7
Current smoker, n (%)	726 (24.5)	125 (27.7)	482 (26.7)	95 (16.3)	24 (18.3)
Pack-years	40.1 ± 23.5	32.3 ± 20.7	39.9 ± 23.2	45.1 ± 24.0	45.2 ± 26.9
Charlson index	1.4 ± 1.3	1.4 ± 1.2	1.2 ± 1.1	1.7 ± 1.4	1.6 ± 1.7
Degree of dyspnoea	1.7 ± 0.9	1.7 ± 0.9	1.5 ± 0.9	2.3 ± 0.9	2.2 ± 1
Post-bronchodilator spirometry					
FVC, l	2.87 ± 0.87	3.03 ± 0.87	2.93 ± 0.86	2.66 ± 0.85	2.48 ± 0.88
FVC, %	69.7 ± 19.2	75.2 ± 19.8	70.3 ± 18.6	64.9 ± 19.1	63.8 ± 19.8
FEV_1, l	1.56 ± 0.59	1.71 ± 0.63	1.6 ± 0.57	1.34 ± 0.56	1.28 ± 0.58
FEV_1, %	53.0 ± 19.0	59.4 ± 20.6	54.0 ± 18.2	46.3 ± 18.0	46.2 ± 18.1
FEV_1/FVC	53.7 ± 11.6	55.3 ± 12.5	54.6 ± 11.0	50.3 ± 11.4	50.1 ± 12.7

Miravitlles M et al, Int J Tuberc Lung Dis. 2015 Aug;19(8):992-8

Demographic And Clinical Characters

Characteristics	ACO (n=42)	ECB (n=188)	EE (n=110)	NE (n=307)	Total (n=647)
Sex (male)*, n (%)	21 (50.0)	157 (83.5)	90 (81.8)	255 (83.1)	523 (80.8)
Age (years)*, mean (SD)	64.2 (9.0)	69.5 (8.6)	70.0 (9.1)	67.2 (9.3)	68.2 (9.2)
BMI (kg/m²)*, mean (SD)	28.0 (5.3)	28.3 (4.5)	26.1 (4.5)	27.2 (4.3)	27.4 (4.5)
Pack-year, mean (SD)	39.4 (17.7)	42.8 (21.2)	48.5 (25.5)	42.9 (23.6)	43.6 (23.0)
Dyspnea (m-MRC scale)*, mean (SD)	1.8 (0.8)	2.1 (0.8)	2.2 (1.0)	1.5 (0.8)	1 .8 (0.9)
Dyspnea scale (m-MRC scale)*, n (%)					
≤1	16 (38.1)	40 (21.5)	27 (24.8)	150 (49.5)	233 (36.4)
≥2	26 (61.9)	146 (78.5)	82 (75.2)	153 (50.5)	407 (63.6)
Respiratory symptoms, n (%)					
Dyspnea on exertion*	37 (88.1)	172 (91.5)	106 (96.4)	255 (83.1)	570 (88.1)
Daily expectorations*	29 (69.1)	171 (91.0)	47 (42.7)	148 (48.2)	395 (61.1)
Wheezing*	30 (71.4)	95 (50.5)	47 (42.7)	75 (24.4)	247 (38.2)
Chronic cough*	36 (85.7)	176 (93.6)	82 (74.6)	193 (62.9)	487 (75.3)
Post-bronchodilator spirometry, mean (SD)					
FEV_1 (mL)*	1,748.0 (679.8)	1,475.0 (503.6)	1,338.4 (544.1)	1,574.1 (599.3)	1,516.5 (577.7)
FEV, (%)*	61.5 (28.1)	54.8 (21.0)	47.9 (16.4)	53.0 (16.2)	53.2 (18.9)

Rubio MC et al, Int J Chron Obstruct Pulmon Dis. 2017; 12: 2373–2383

FENEPOC – Treatment Characteristics

Treatment, n (%)	ACO (n=42)	ECB (n=188)	EE (n=110)	NE (n=307)	Total (n=647
LABA (only monotherapy)	0 (0.0)	1 (0.5)	0 (0.0)	11 (3.6)	12 (1.9)
LAMA (only monotherapy)	2 (4.8)	2 (1.1)	1 (0.9)	26 (8.5)	31 (4.8)
SABA (only monotherapy)	0 (0.0)	1 (0.5)	1 (0.9)	1 (0.3)	3 (0.5)
SABA + SAMA	0 (0.0)	2 (1.1)	1 (0.9)	4 (1.3)	7 (1.1)
LABA + LAMA (free or fixed dose combination)	2 (4.8)	33 (17.6)	20 (18.2)	98 (31.9)	153 (23.6)
LABA + LAMA + ICS (free combination)	25 (59.5)	109 (58.0)	64 (58.2)	88 (28.7)	286 (44.2)
LABA + ICS (free or fixed dose combination)	9 (21.4)	8 (4.3)	10 (9.1)	19 (6.2)	46 (7.1)
LAMA + ICS (free combination)	0 (0.0)	13 (6.9)	6 (5.5)	9 (2.9)	28 (4.3)
Other treatments*	4 (9.5)	17 (9.0)	7 (6.4)	48 (15.6)	76 (11.7)
No treatment	0 (0.0)	2 (1.2)	0 (0.0)	3 (1.0)	5 (0.8)

Note: *Other treatments comprised combinations of Roflumilast, theophylline, systemic corticosteroids, antibiotics and/or mucolytics.

Rubio MC et al, Int J Chron Obstruct Pulmon Dis. 2017; 12: 2373–2383

Miravitlle's- Treatment Characteristics

Treatment	Total ($n = 3125$) n (%)	ACOS patients ($n = 496$) n (%)	Non-exacerbators ($n = 1894$) n (%)	Exacerbators with chronic bronchitis ($n = 602$) n (%)	Exacerbators without chronic bronchitis ($n = 133$) n (%)
SABA	1292 (44.2)	185 (42.2)	713 (40.3)	328 (56.1)	66 (51.6)
LABA	2459 (84.2)	359 (82)	1442 (81.5)	545 (93.2)	113 (88.3)
SAMA	253 (8.7)	46 (10.5)	120 (6.8)	75 (12.8)	12 (9.4)
LAMA	2096 (71.8)	257 (58.7)	1260 (71.2)	477 (81.5)	102 (79.7)
Theophylline	135 (4.6)	21 (4.8)	54 (3.1)	48 (8.2)	12 (9.4)
Inhaled corticosteroids	2034 (69.7)	337 (76.9)	1090 (61.6)	504 (86.2)	103 (80.5)
Oral corticosteroids	171 (5.9)	30 (6.8)	42 (2.4)	87 (14.9)	12 (9.4)
Roflumilast	168 (5.8)	20 (4.6)	65 (3.7)	70 (12)	13 (10.2)
Mucolytics	705 (24.1)	153 (34.9)	299 (16.9)	235 (40.2)	18 (14.1)
LTOT	335 (11.5)	29 (6.6)	125 (7.1)	146 (25)	35 (27.3)

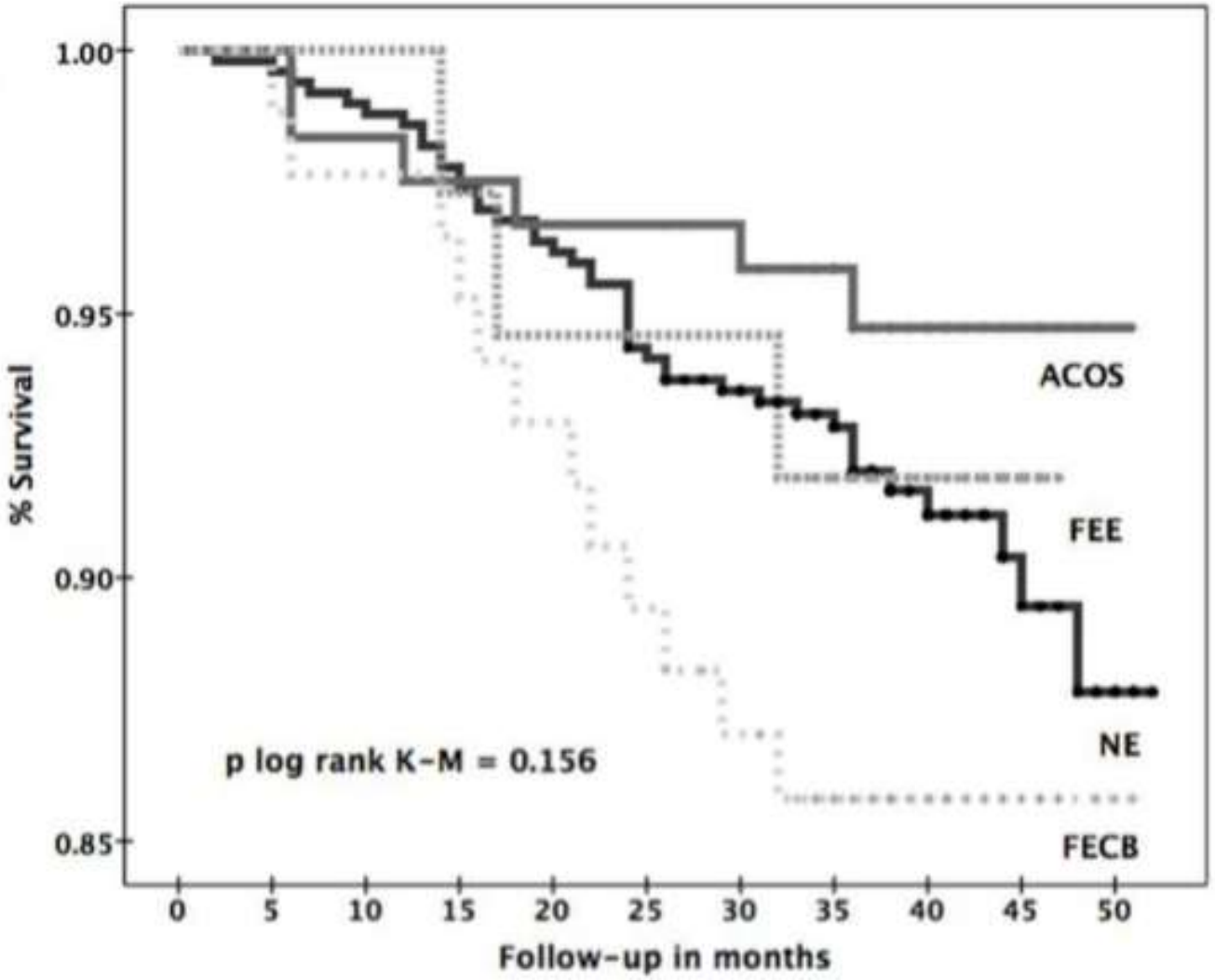
Miravitlles M et al, Int J Tuberc Lung Dis. 2015 Aug;19(8):992-8

CHAIN cohort- Treatment Characteristics

	0	NE	ACOS	FEE	FECB	p
	19 (2.3%)	**550 (66.2%)**	**125 (15.0%)**	**38 (4.6%)**	**99 (11.9%)**	
Anticholinergics, n (%)	18 (94.7)	398 (72.5)	82 (65.6)	33 (86.8)	88 (88.9)	<0.001
Beta2-agonists, n (%)	15 (78.9)	396 (72.0)	91 (72.8)	32 (84.2)	85 (85.9)	0.029
Inhaled steroids, n (%)	14 (73.7)	344 (62.5)	79 (63.2)	29 (76.3)	78 (78.8)	0.009
Theophylline, n (%)	6 (31.6)	43 (7.8)	6 (4.8)	4 (10.5)	18 (18.2)	<0.001

Cosio BG et al, PLoS One. 2016 Sep 29;11(9):e0160770

Survival - phenotypes



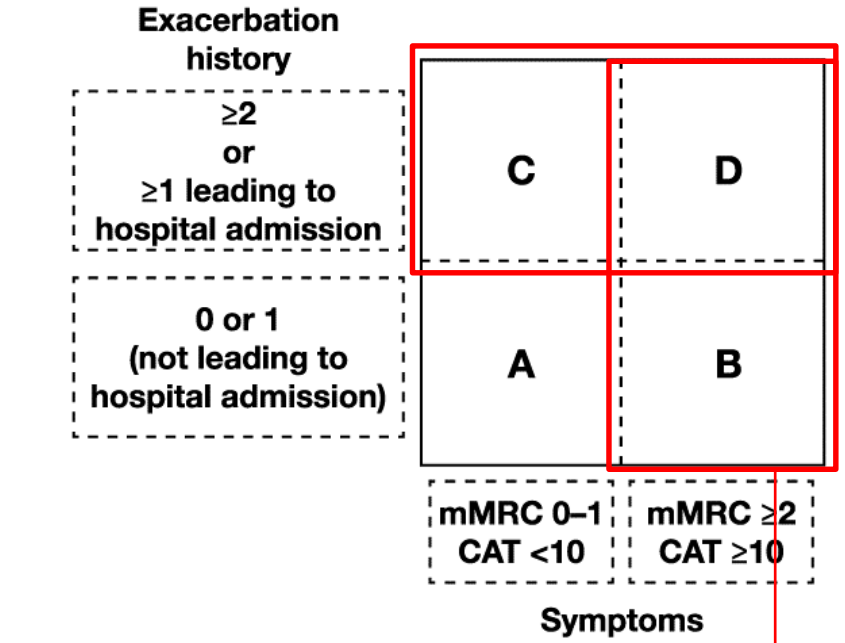
Cosio BG et al, PLoS One. 2016 Sep 29;11(9):e0160770

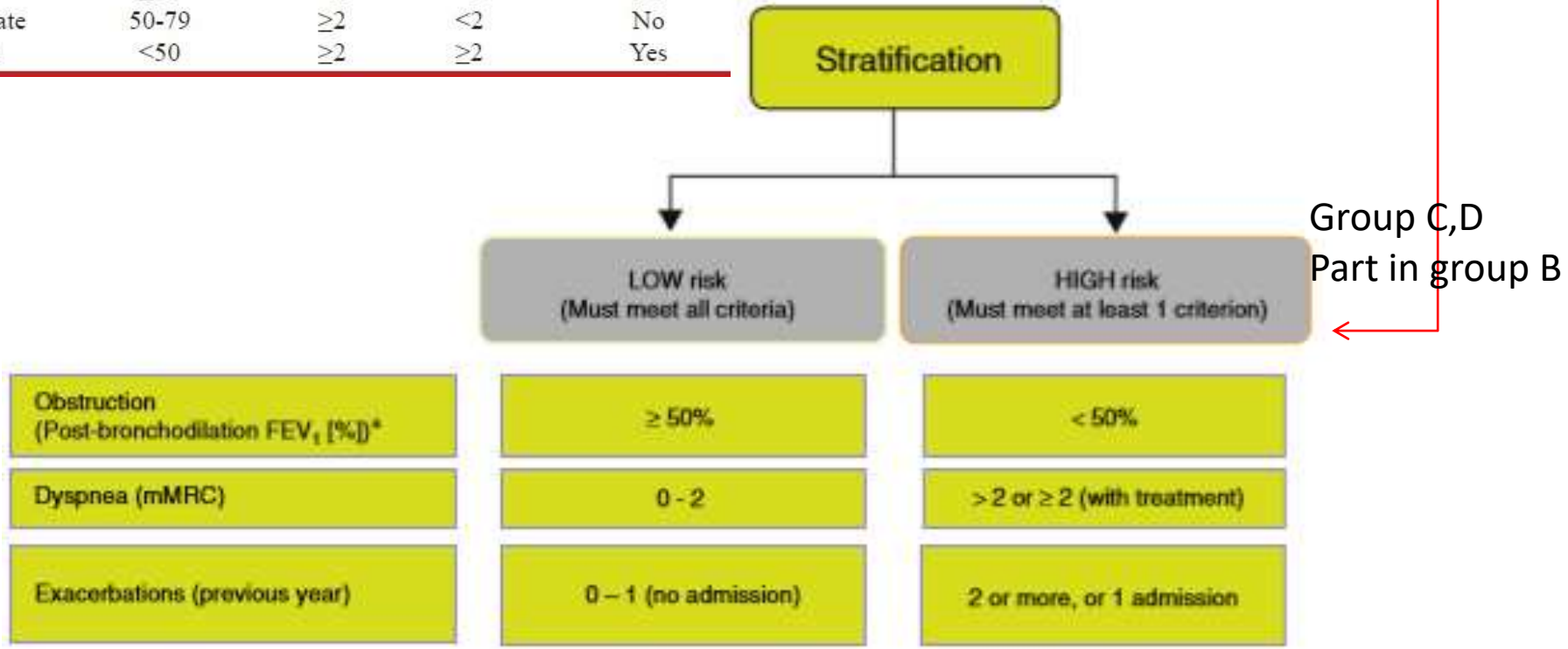
COMPARING GOLD AND CLINICAL PHENOTYPE BASED GROUPING AND TREATMENT APPROACH

Post-bronchodilator $FEV_1/FVC < 0.7$

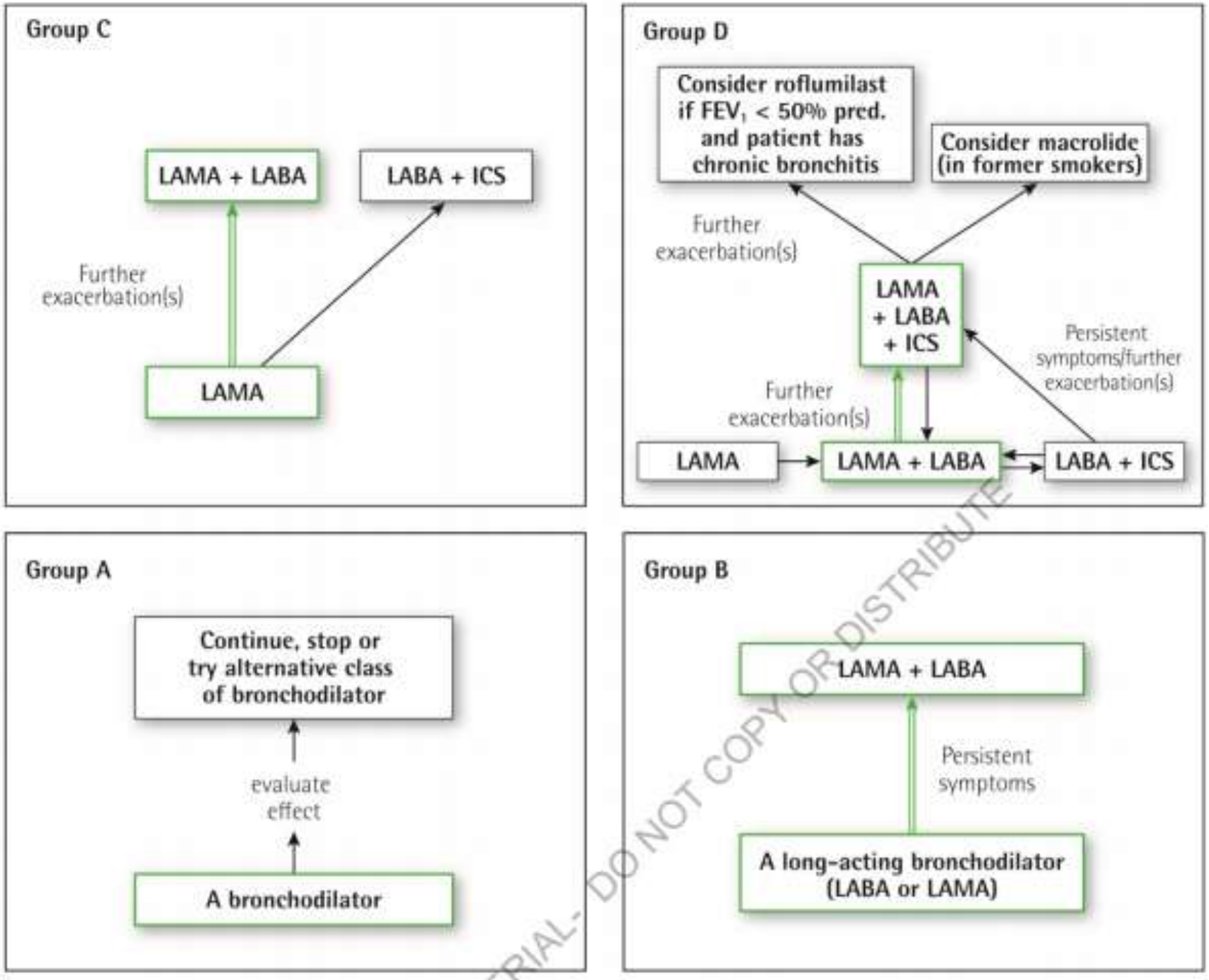
	FEV_1 (% of predicted)
GOLD 1	≥80
GOLD 2	50–79
GOLD 3	30–49
GOLD 4	<30

Severity*	Postbronchodilator FEV_1, % predicted	mMRC grade	Exacerbation frequency†	Complications‡
Mild	≥80	<2	<2	No
Moderate	50-79	≥2	<2	No
Severe	<50	≥2	≥2	Yes

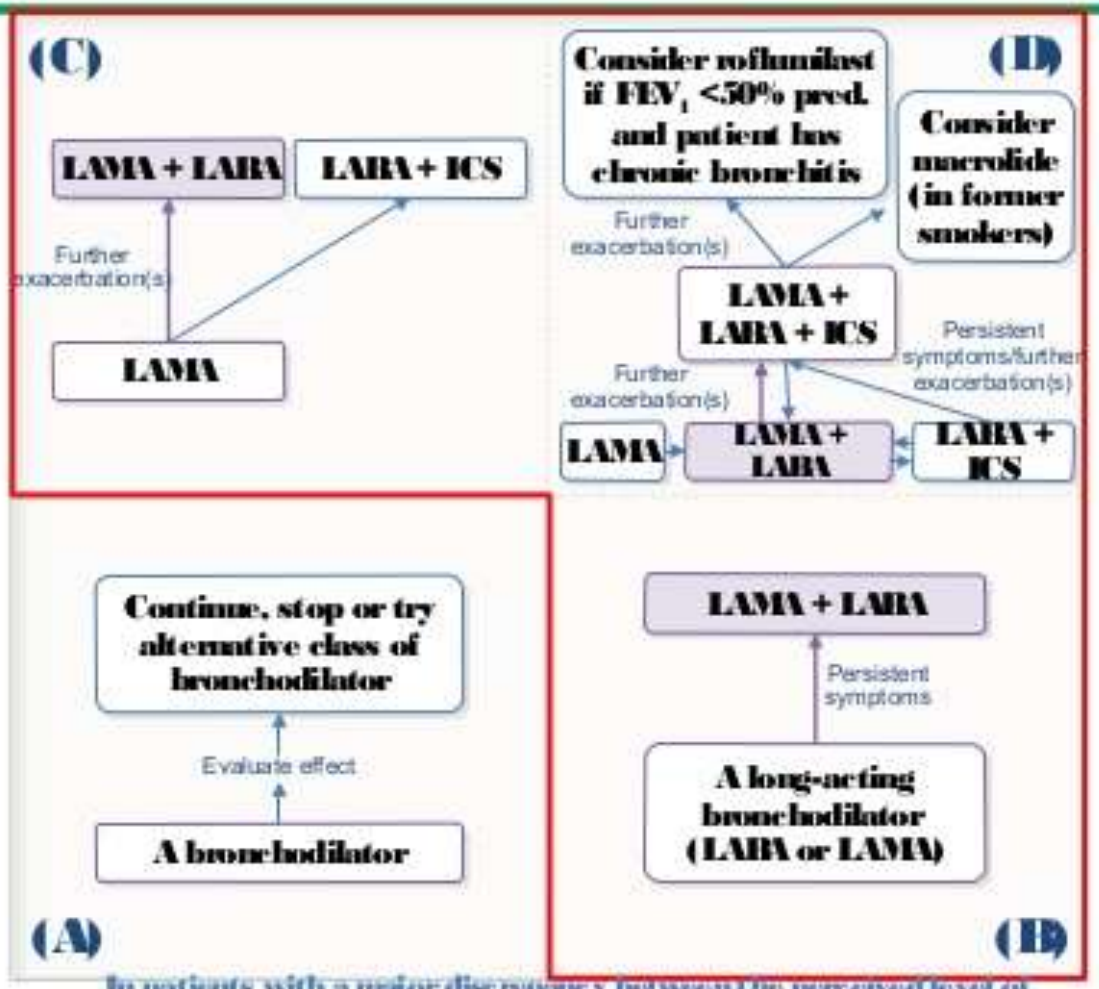




Group C,D
Part in group B



Treatment algorithm by GOLD groups: LAMA/LABA plays a central role for GOLD B-D

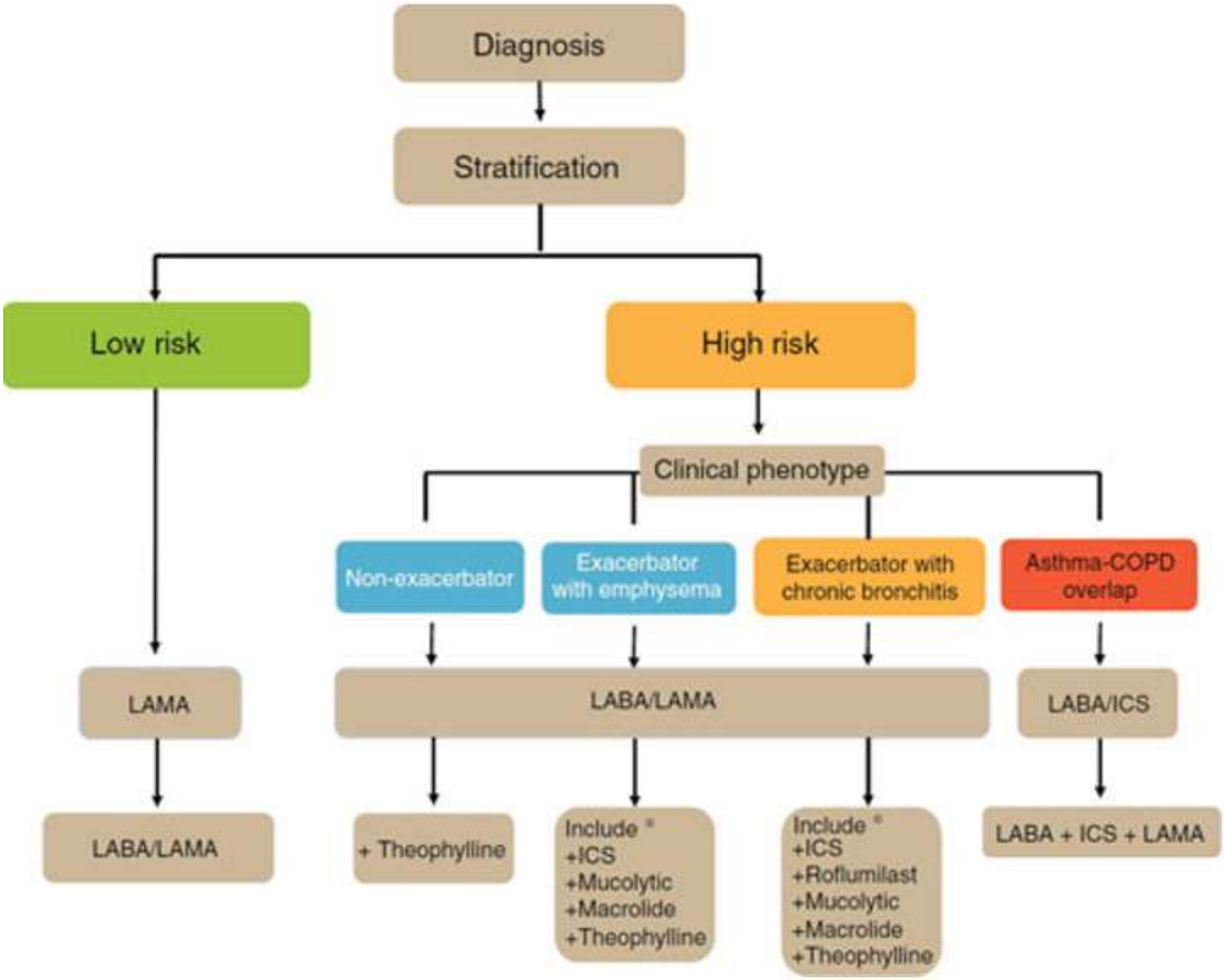


In patients with a major discrepancy between the perceived level of symptoms and severity of airflow limitation, further evaluation is warranted

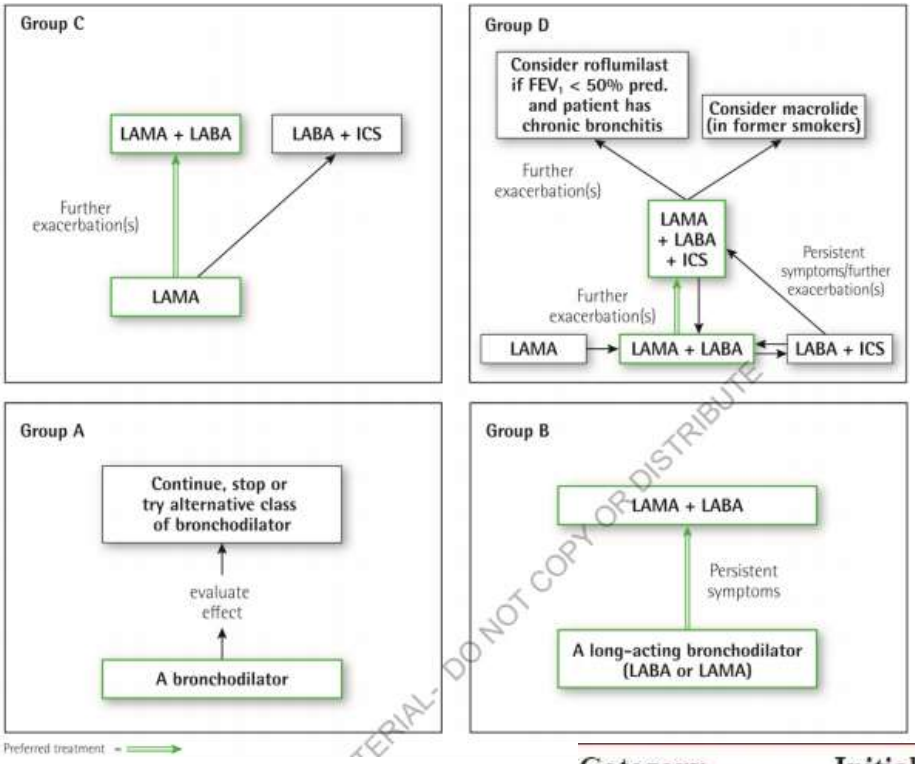
LAMA/LABA plays a critical, central role for GOLD B-D

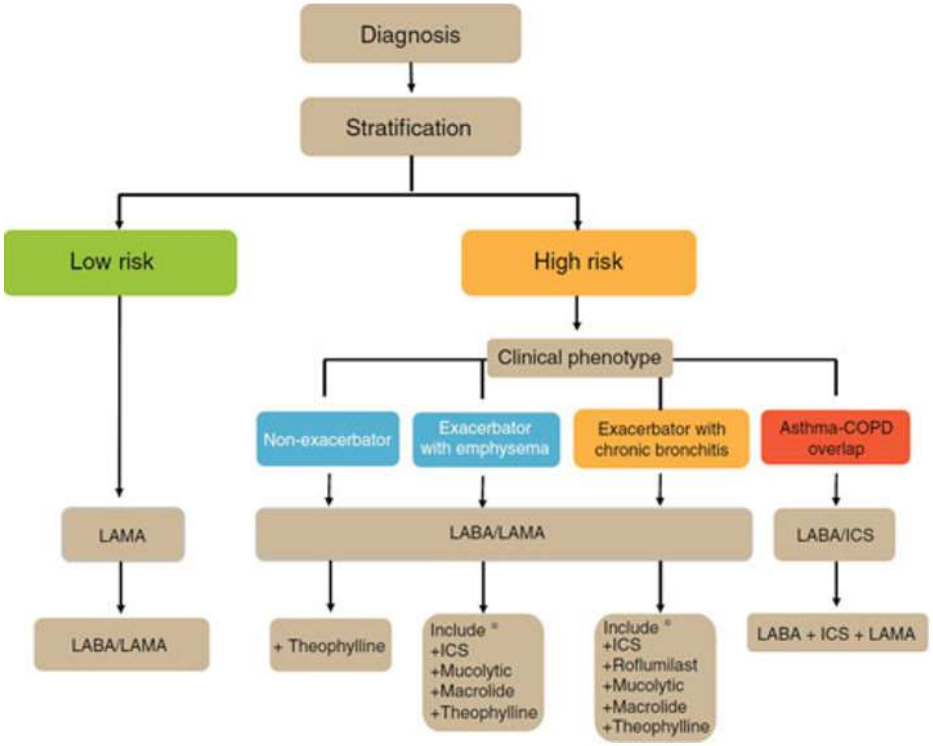
For GOLD B patients with severe breathlessness initial therapy with two bronchodilators may be considered

↑ Preferred treatment


Diagnosis
Stratification
Low risk
High risk
Clinical phenotype
Non-exacerbator
Exacerbator with emphysema
Exacerbator with chronic bronchitis
Asthma-COPD overlap
LAMA
LABA/LAMA
LABA/ICS
LABA/LAMA
+ Theophylline
Include *
+ICS
+Mucolytic
+Macrolide
+Theophylline
Include *
+ICS
+Roflumilast
+Mucolytic
+Macrolide
+Theophylline
LABA + ICS + LAMA

Treatment

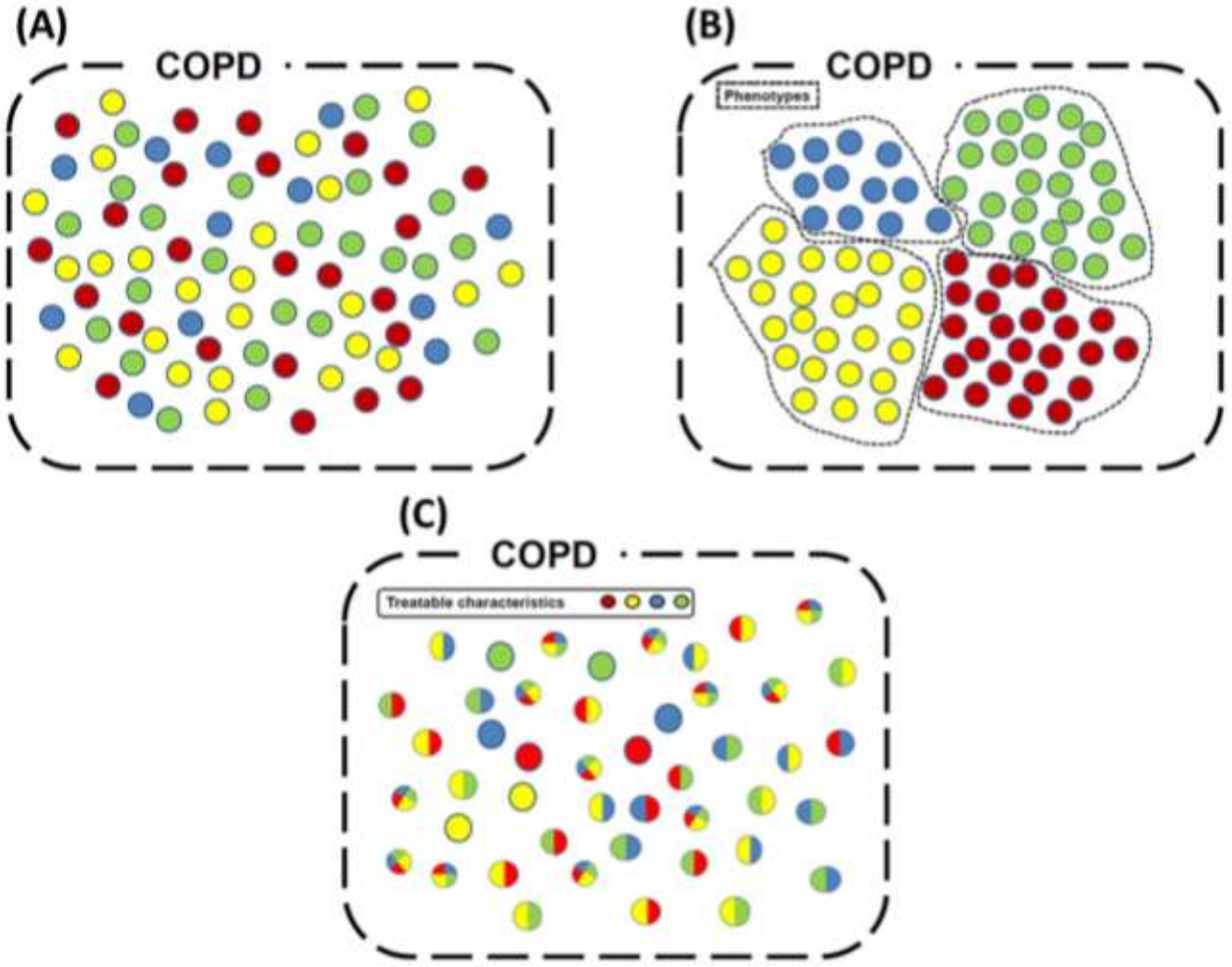




Group A→ Low risk
Group B,C,D → High risk

Category	Initial therapy		Add-on therapy (if patient continues to have symptoms)
	First choice	Alternative choice	
Mild	SABA or SAMA prn	Methyl xanthines	-
Moderate	LAMA	LABA	Methylxanthines to LAMA/ LABA
Severe	ICS plus LABA	LAMA	Methylxanthines to LAMA or ICS plus LABA

Temporal evolution of the understanding and management of chronic obstructive pulmonary disease



Each node – theoretical patient
Each colour – clinical characteristic

Pharmacogenetic testing ??

Gene	N	Variant(s)	Phenotype*	Study	Comments
ACE	206†	rs4646994	Hospitalisation records	Mlak *et al*[10]	Deletion variant protective among males
ADRB2	5125	rs1042713 rs1042714	Prospective moderate-to-severe AE (steroids/ antibiotic treatment)	Rabe *et al*[11]	Pharmacogenetic study; Major allele of rs1042713 associated with decreased risk of AE in salmeterol-treated group
ADRB2	190†	rs1042713 rs1042714	'Frequent' exacerbators (≥3 hospitalisations within 1 year) vs 'Stable' (0 in 2 years)	Vacca *et al*[12]	No association reported
ADRB2	92	rs1042713 rs1042714	Self-reported exacerbations during the 12 months prior to enrolment	Emeryk-Mksymiuk *et al*[13]	Major allele of rs1042713 associated with increased risk of AE
EPHX1	219	rs1051740 rs2234922	Moderate-to-severe AE for 1 year with administration of oral *N*-acetylcysteine	Zhang *et al*[14]	Pharmacogenetic study; 'slow' enzyme activity group with lower exacerbation rate than 'fast activity' group
F2R	203†	rs2227744	Diary card exacerbations— dichotomised 'frequent' (≥3) vs 'infrequent' (<3)	Platé *et al*[15]	Minor allele protective for frequent exacerbations
GC	135†	rs4588 rs7041	Diary card exacerbations (count)	Ishii *et al*[16]	rs4588 variants associated with increased frequency of exacerbations
HMOX1	368	Long (>32) dinucleotide repeats	Moderate-to-severe AE for 1 year with administration of oral *N*-acetylcysteine	Zhang *et al*[17]	Pharmacogenetic study; absence of long dinucleotide repeats protective
MBL2	200†	rs1800450	Hospital admissions by medical record review+telephone confirmation	Yang *et al*[6]	Minor allele associated with lower systemic MBL levels and increased risk for AE
MBL2	215	rs11003125 rs7096206 rs5030737 rs1800450 rs1800451	Moderate-to-severe AEs assessed by interview+record review for 3 years following enrolment. 'Recurrent' vs 'less frequent'	Lin *et al*[4]	Decreased serum MBL levels and increased proportion of MBL2 deficiency haplotypes among 'recurrent' exacerbators

Wan ES, Thorax. 2018 Jun;73(6):507-509

Pharmacogenetic testing ??

MBL2	277	rs11003125 rs7096206 rs7095891 rs5030737 rs1800450 rs1800451	Moderate-to-severe AEs by interview, medical records and public registry data. 'Frequent' (≥2/year) vs 'infrequent' (<2/year)	Mandal *et al*[5]	MBL2 deficiency haplotypes more common in 'frequent' exacerbators, however, no correlation with systemic MBL levels and exacerbation phenotypes
NR3C1	207†	rs56149945 rs41423247 rs6189 rs6190	'Unstable' (≥3 hospitalisations) vs 'stable'	Schwabe *et al*[18]	No association reported
SIGLEC9	135	rs2075803 rs2258983	Diary card exacerbations (count)	Ishii *et al*[19]	Minor allele of rs2075803 associated with increased risk of AE. Did not replicate in larger study
SIGLEC14	135	Null allele	Prospective interviews—mild to severe AEs recorded	Angata *et al*[20]	Null allele associated with decreased risk of AE
SERPINA1	204†	11478G→A	Diary card exacerbations—dichotomised 'frequent' (≥3) vs 'infrequent' (<3)	Quint *et al*[21]	No association reported
SFTPB	389	rs2118177 rs2304566 rs1130866 rs3024791	Emergency room visits and hospitalisations	Foreman *et al*[22]	SFTPB variants associated with AE. Variants in EPHX1, GSTP1, TGFB1, SERPINE2 also examined but demonstrated no associations
SFTPD	192†	rs911887 rs2243639 rs10887199 rs2255601 rs721917 rs726288	Emergency room visits and hospitalisations—dichotomised 'high' (≥2) vs 'low' (<2)	Ou *et al*[23]	No association with haplotypes reported
TNF	60†	rs1800629	Retrospective moderate-to-severe AE year prior	Özdoğan *et al*[24]	No association reported

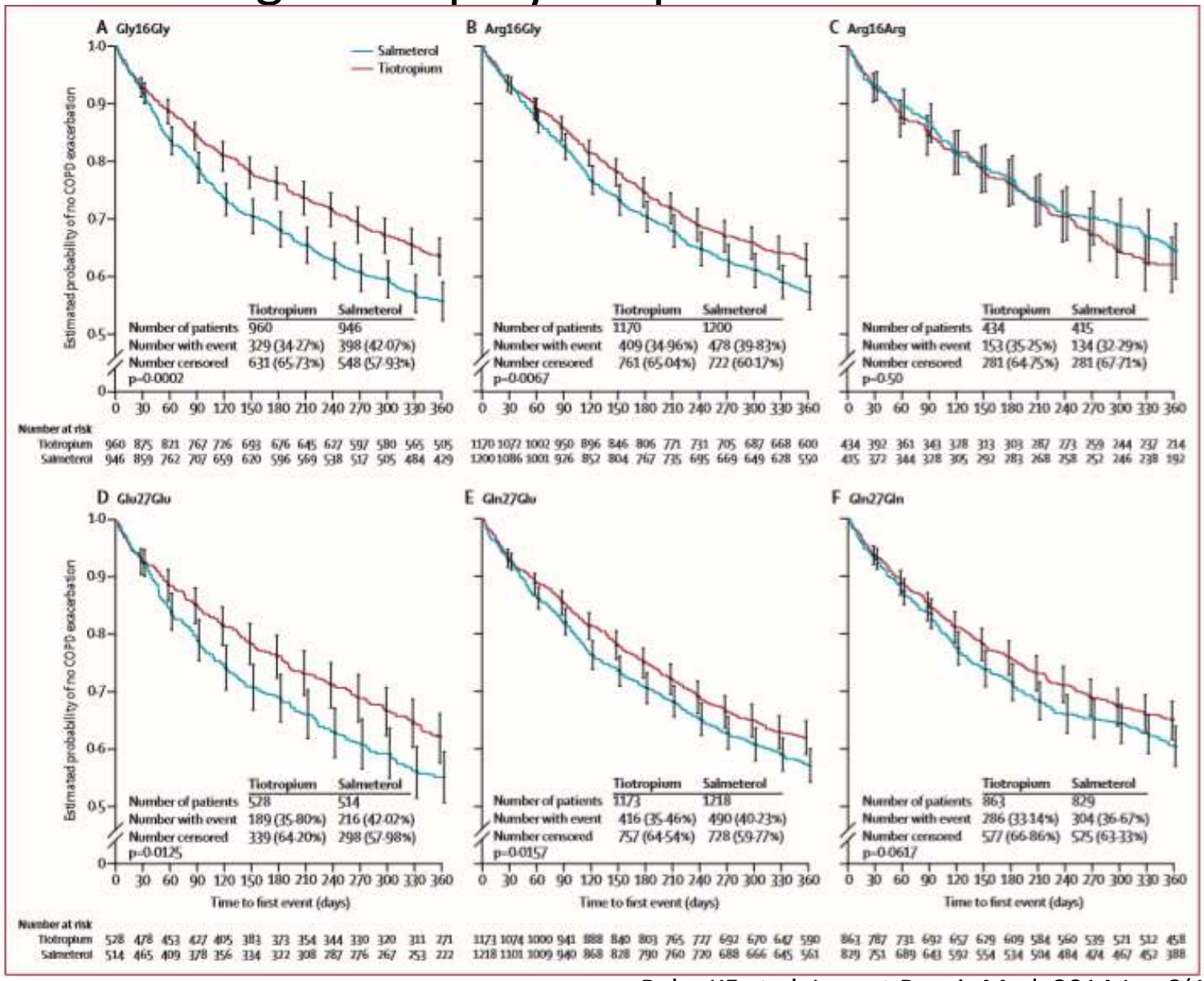
Wan ES, Thorax. 2018 Jun;73(6):507-509

Pharmacogenetics

- Of 7376 patients with COPD POET-COPD trial
- Prespecified analysis in 5125 (who gave consent)
- Polymorphisms of the β2-adrenergic receptor (ADRB2) gene
  - Arg16Gly (rs1042713)
  - Gln27Glu (rs1042714)
    - influenced the effect of LABD
    - tiotropium vs salmeterol in the prevention of exacerbations

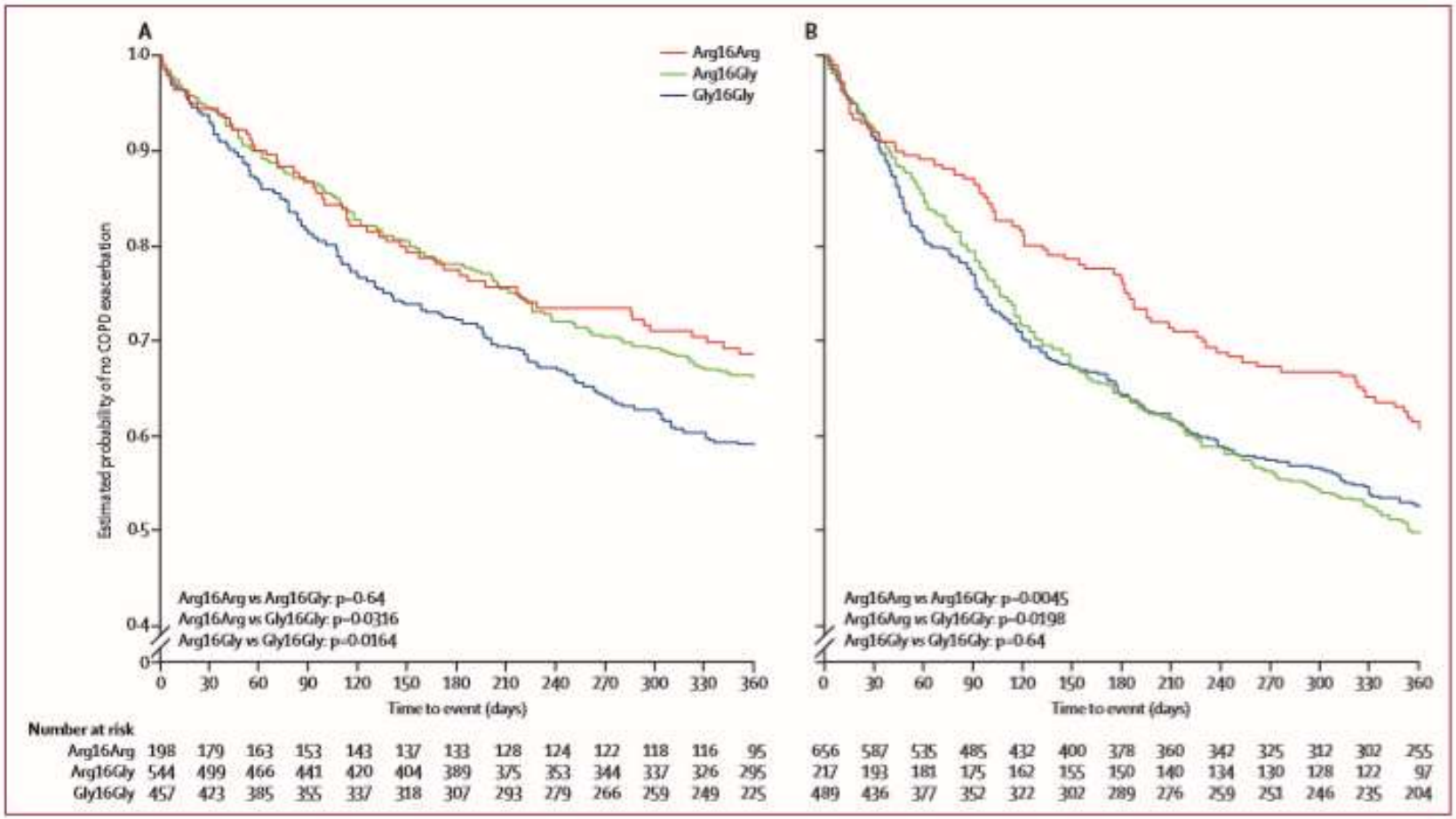
Rabe KF et al, Lancet Respir Med. 2014 Jan;2(1):44-53

LABA Vs LAMA – Rate of exacerbations & genetic polymorphisms



Rabe KF et al, Lancet Respir Med. 2014 Jan;2(1):44-53

Influence of ICS – LABD Gene Polymorphisms



Rabe KF et al, Lancet Respir Med. 2014 Jan;2(1):44-53

Take home message

- COPD phenotype based treatment may be attempted
  - Spanish guidelines
  - Grossly similar to present GOLD recommendations
- Dual LABD → add on ICS
- ACOS and eosinophilic COPD
  - ICS in addition to LABD as first line Rx
  - Mepolizumab role in eosinophilic COPD is not clear
- Frequent exacerbators
  - Roflumilast (chronic bronchitis phenotype)
  - Mucolytics/macrolides
- Future treatment
  - To include pharmacogenetics