Triple therapies: opening spaces for hope in COPD patients

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Presenter disclosures

Alberto Papi

- Personal financial relationships with commercial interests relevant to medicine, within past 3 years:
  - *Consultant or Advisory Board or Board Member:* AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Mundipharma, Novartis IT, Zambon, Almirall, TEVA
  - *Lecture Fees:* AstraZeneca, Chiesi Farmaceutici, Boehringer Ingelheim, GlaxoSmithKline,
    Gentili, Pfizer, Merck Sharp & Dohme, Novartis, Mundipharma, Novartis, Almirall, TEVA
  - *Industry-Sponsored Grants:* AstraZeneca, Chiesi Farmaceutici, Boehringer Ingelheim, GlaxoSmithKline, Merck Sharp & Dohme, Menarini, Fondazione Maugeri, Fondazione
    Chiesi Farmaceutici

- Member of GOLD Science Committee
- No relationships with tobacco entities
- No non-commercial relationship to disclosures

Triple therapies: opening spaces for hope in COPD patients

- Definitions & treatment outcomes.
- Exacerbations and their prevention
  - GOLD 2019-20
- New options, new hopes
  - Triple Therapy: Efficay safety
- ….and beyond: new hopes
- In addition….. Letters..

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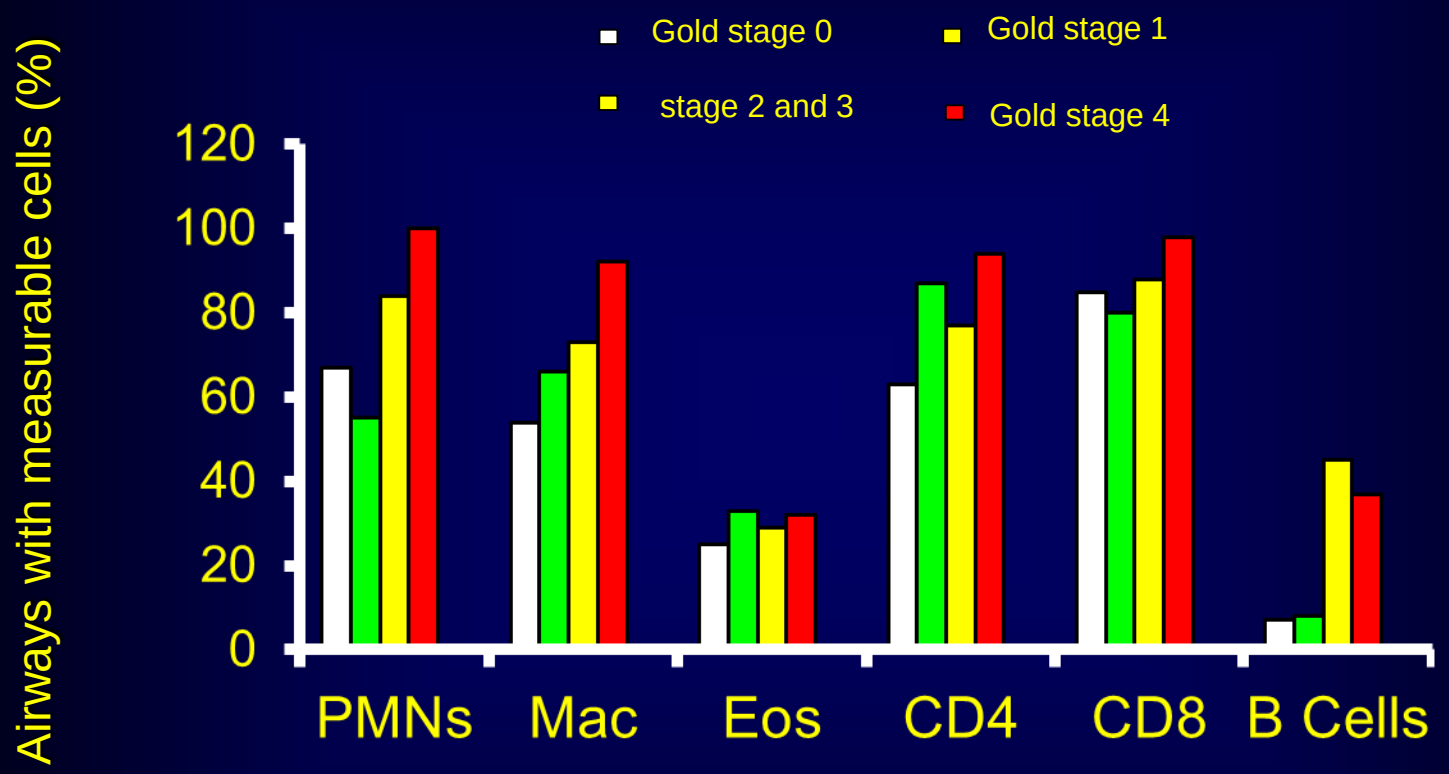
DEFINITION GOLD 2020

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 including abnormal lung development. Significant comorbidities may have an impact on morbidity and mortality.

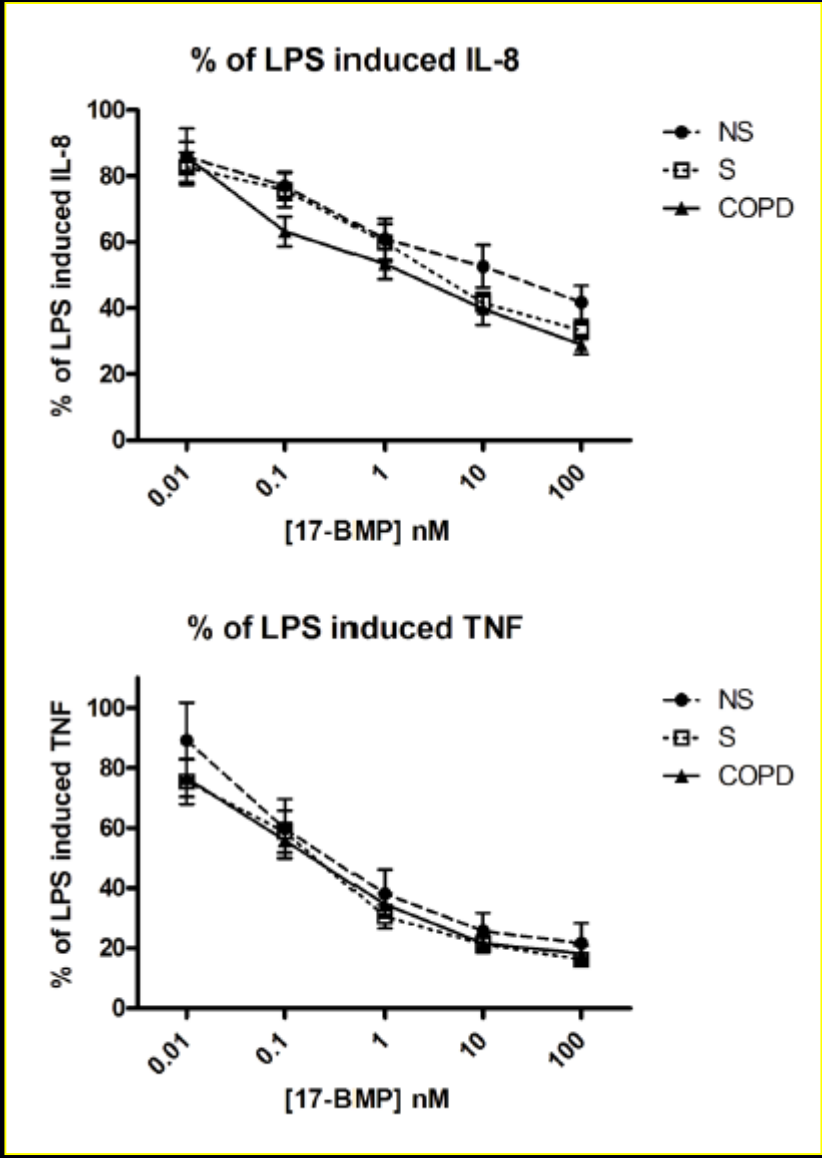
- The chronic airflow limitation **that is characteristic of COPD is caused by a** mixture of small airways disease (**e.g., obstructive bronchiolitis**) and parenchymal destruction **(emphysema),** the relative contributions of which vary from person to person.
- Chronic inflammation causes structural changes, *narrowing of the small airways and destruction of the lung parenchyma that leads to the loss of alveolar attachments to the small airways and decreases lung elastic recoil. In turn, these changes diminish the ability of the airways to remain open during expiration.* A loss of small airways may also contribute to airflow limitation

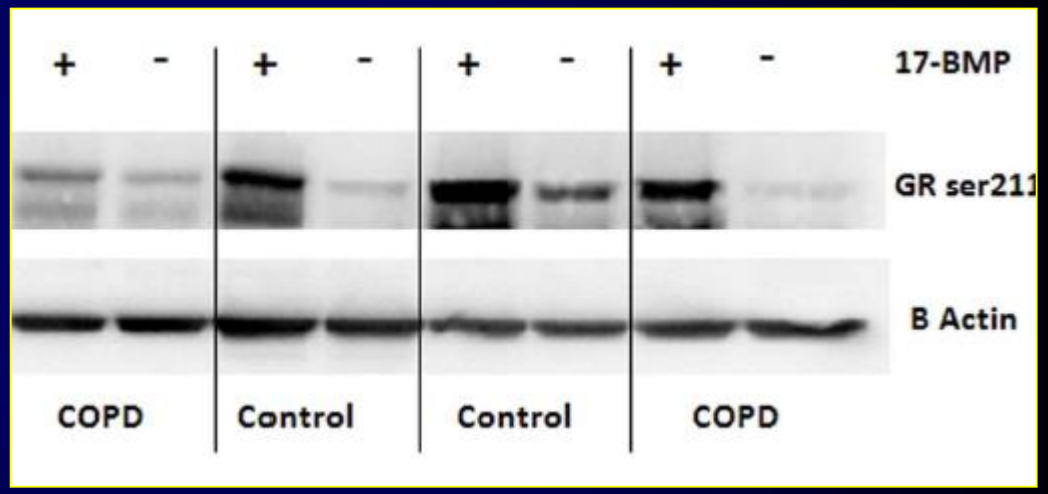
Inflammation and severity



(Hogg et al NEJM 2004)

Effects of 17-BMP on LPS-stimulated cytokines



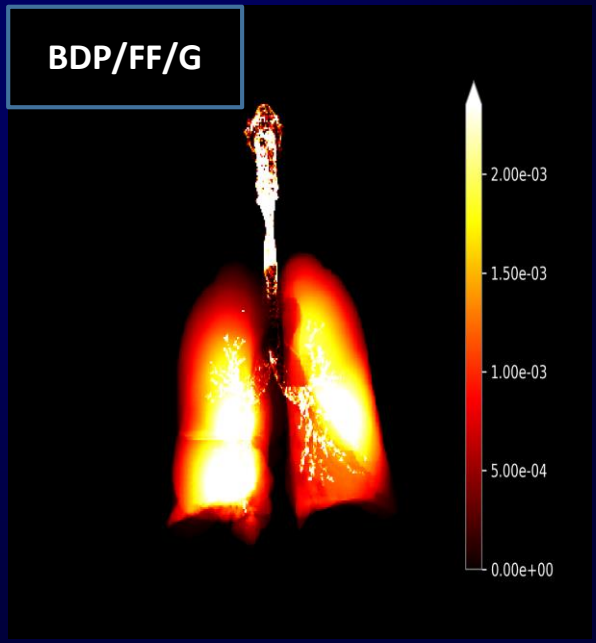


Plumb J, PLoS ONE 2013

Lung deposition of extrafine triple therapy in patients with COPD by Functional Respiratory Imaging (FRI)

AIMS: To evaluate **lung deposition patterns of extrafine formulation BDP/FF/G pMDI** in patients with stable COPD and moderate to very severe airflow obstruction.

METHODS: Intrathoracic depositions of ICS, LABA, and LAMA components were calculated in **20 patients**. Inhalation was simulated in silico using a per-patient profile derived from real life measurement.

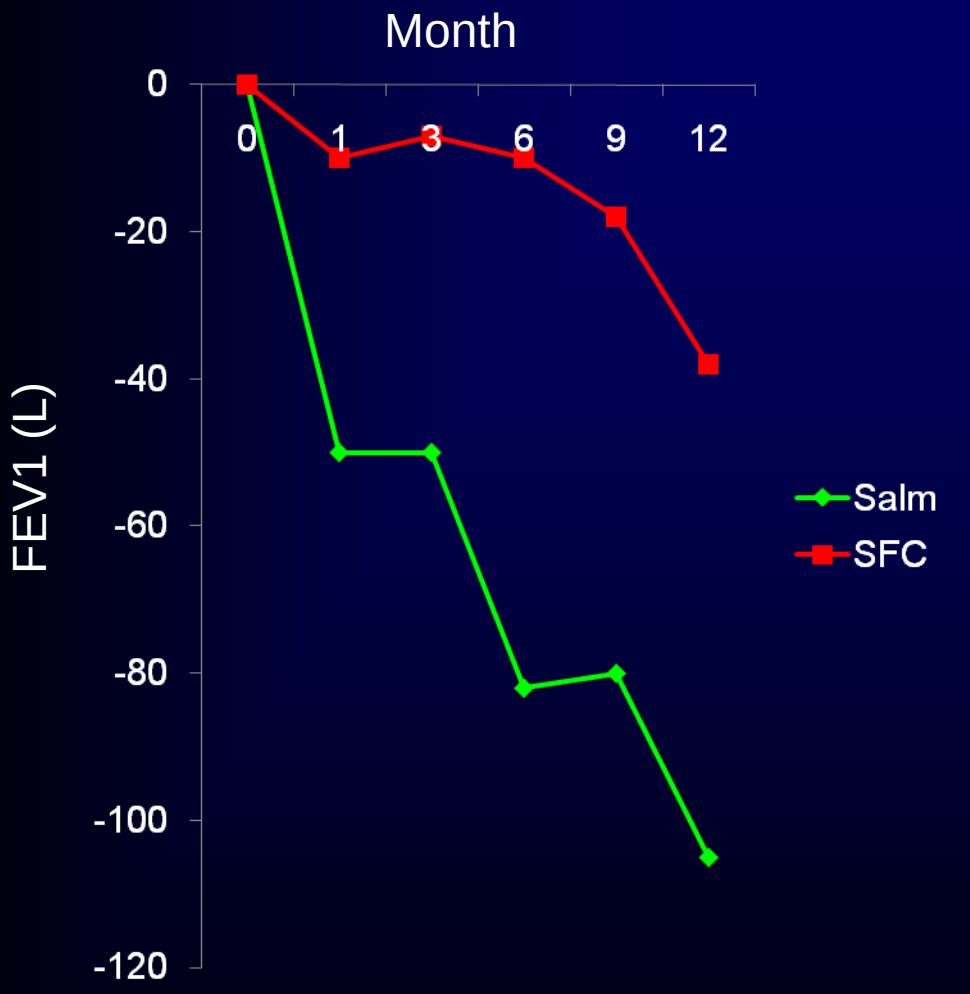


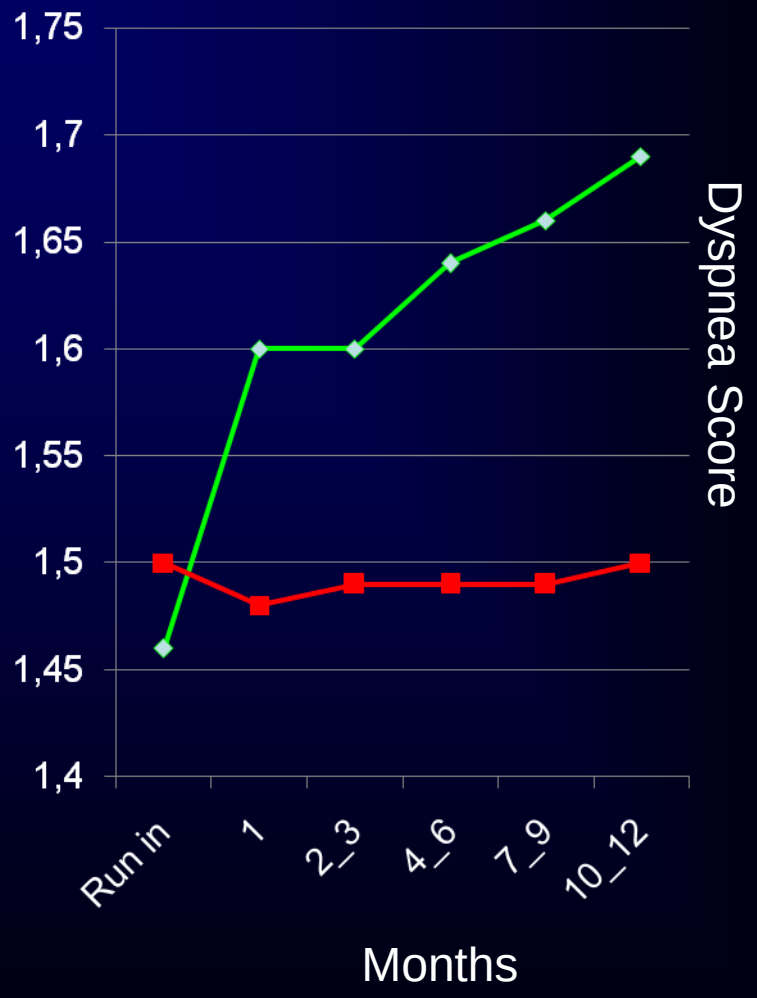
Component	Extrafine formulation BDP/FF/G pMDI
ICS	0.48 +/- 0.13
LABA	0.48 +/- 0.13
LAMA	0.49 +/- 0.13

Central to peripheral deposition ratios (all flow rates)

Usmani et al., ERS Congress 30th September 2019 (Madrid)

Withdrawal of FP from SFC





Wouters, Thorax 2005

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

Making Sense of Triple Inhaled Therapy for COPD

Samy Suissa, Ph.D., and Jeffrey M. Drazen, M.D.

….% of the patients enrolled in the trial were receiving treatment with triple therapy……

Thus, for the patients assigned to the LAMA–LABA group, many of whom were actually *stepping down in their treatment, inhaled glucocorticoids were abruptly withdrawn at the time of randomization; this could lead to COPD exacerbations*.[7-9]

7. Suissa S, et al. Eur Respir J 2008.
8. Vestbo J, et al Clin Respir J 2011
9. Suissa S. Thorax 2014.

N Engl J Med , May 2018

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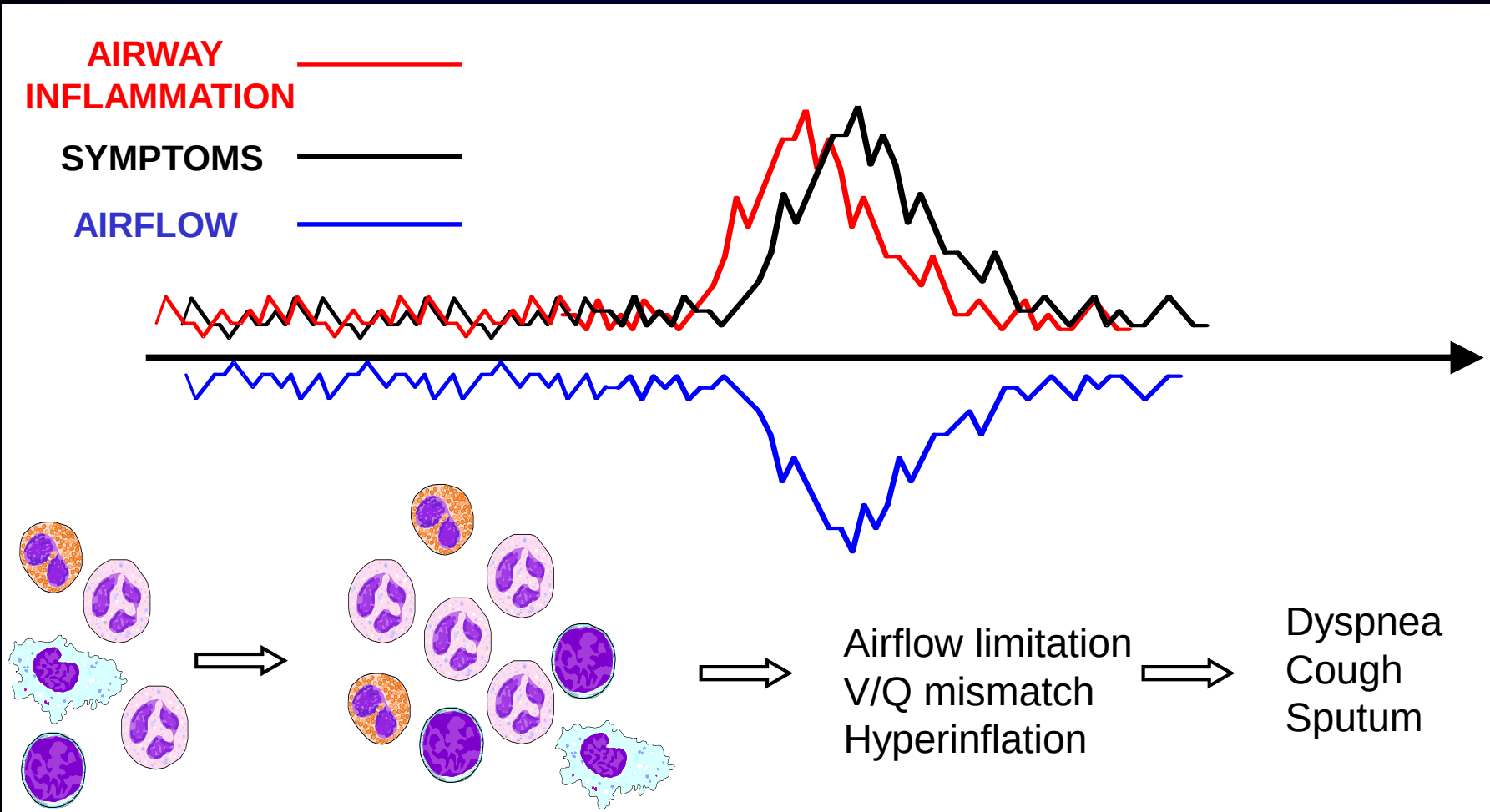
COPD exacerbations: Definition

COPD exacerbations are defined as an acute worsening of respiratory symptoms that result in additional therapy. They are classified as mild (treated with short acting bronchodilators only, SABAs), moderate (treated with SABAs plus antibiotics and/or oral corticosteroids) or severe (patient requires hospitalization or visits the emergency room). Severe exacerbations may also be associated with acute respiratory failure , ….

GOLD Report 2019

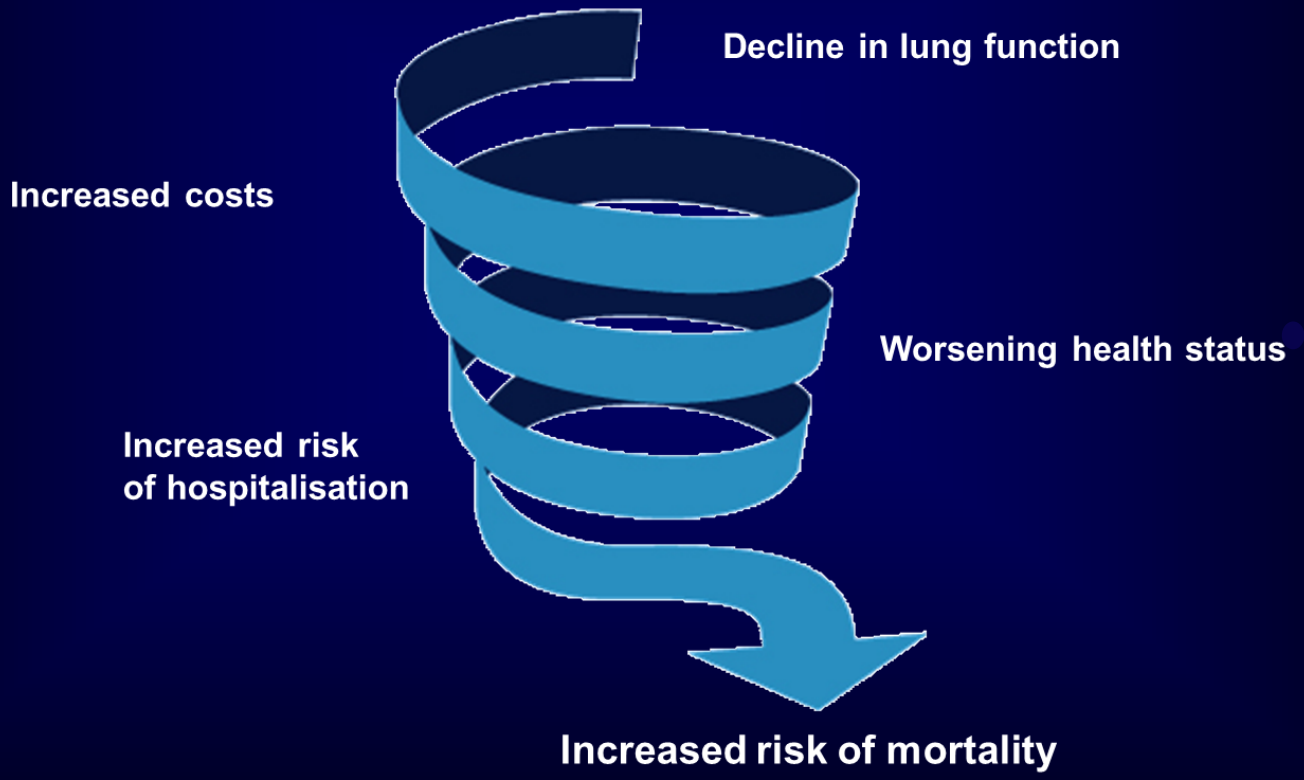
Pathogenesis of COPD exacerbations



Mallia et al., AJRCCM, 2011
Papi et al., Proc Am Thorac Soc, 2006

Exacerbations drive morbidity and mortality

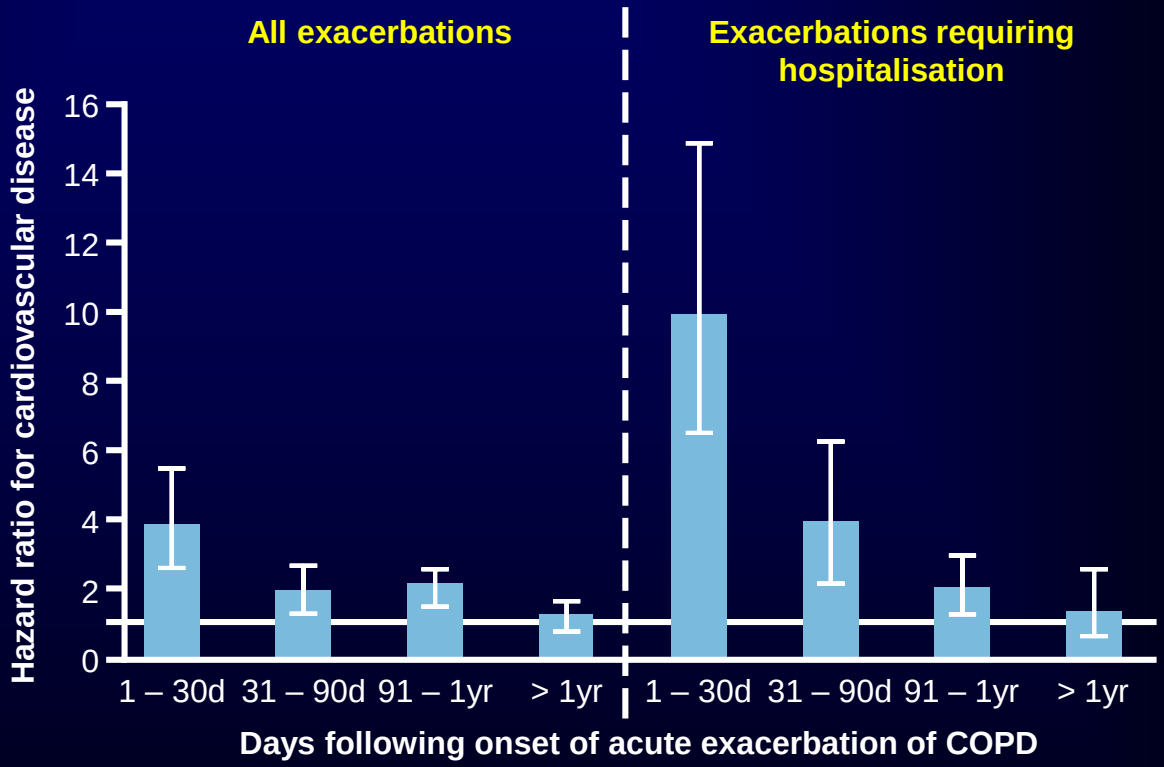
COPD exacerbations lead to:



GOLD Report 2019

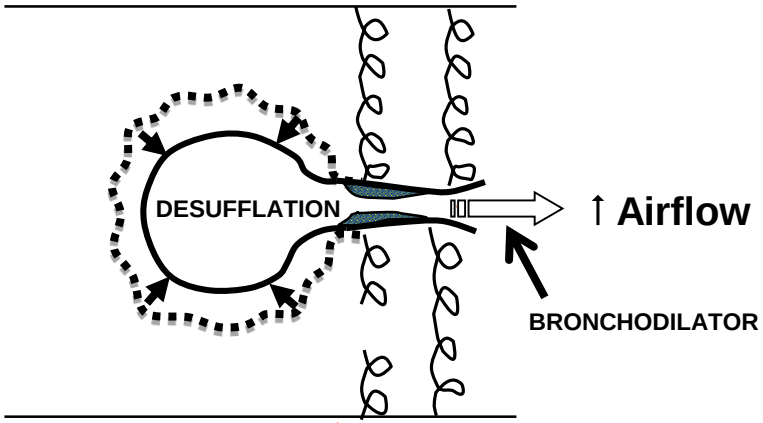
Cardiovascular events following an acute COPD exacerbation

Cardiovascular disease
- Myocardial infarction
- Stroke
- Unstable angina
- Transient ischaemic attack
- Cardiovascular death



Adapted from Kunisaki KM, et al. *Am J Respir Crit Care Med.* 2018;198:51–57.

Bronchodilators & “desufflation”



→ Increase: time integrate flow: ↑ FEV_1

→ Lung volumes: ↓ RV, FRC, PEEPi

↑ VC, IC

→ Decreased dyspnoea (chronic and exercise)

→ Increased exercise tolerance

Comparison of reduction of COPD exacerbation rate observed in recent studies of ICS/LABA combinations vs LABA monotherapy

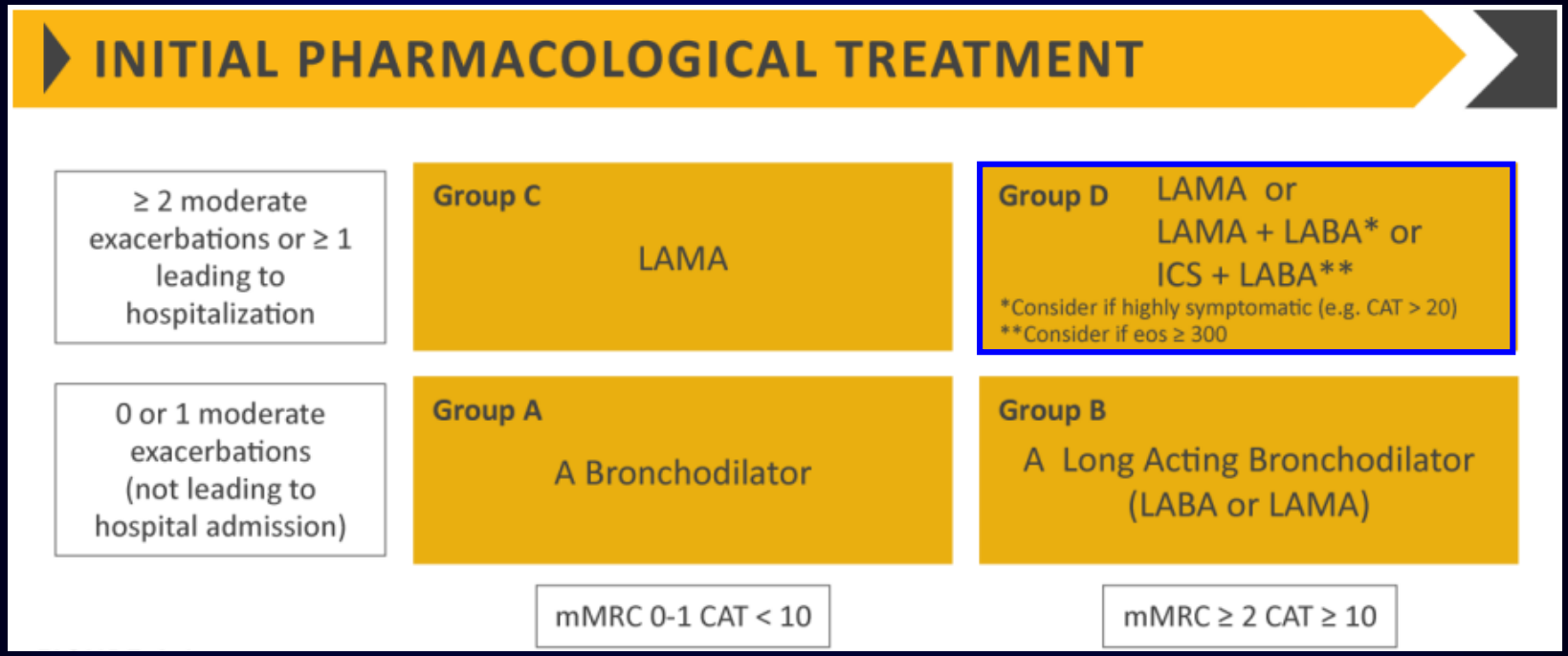
- ICS/LABAs show a consistent reduction of approx 25-30% vs LABAs
- A Cochrane meta- analysis reports an average 24% reduction in exacerbations with ICS/LABAs vs LABAs[1]

Study reference	Drugs and total daily dose (µg)	Study duration	Annual rate of moderate/severe exacerbations		
			ICS/LABA	LABA	Reduction ICS/LABA vs LABA (%)
Calverley et al	FP/Salm 1000/100 vs Salm 100	3 years	0.85	0.97	12[a]
Szafranski et al	BUD/FF 800/24 vs FF 24	12 months	1.42	1.84	23[a]
Rennard et al	BUD/FF 400/12 vs FF 12	12 months	n/a	n/a	25[a]
Calverley et al	BUD/FF 800/24 vs FF 24	12 months	1.38	1.85	25.5[a]
Sharafkhaneh et al	BUD/FF 200/12 vs FF 12	12 months	0.79	1.07	25.9[a]
Wedzicha et al	BDP/FF 400/24 vs FF 24	48 weeks	0.80	1.12	28.1[a]
Rennard et al	BUD/FF 200/12 vs FF 12	12 months	n/a	n/a	29[a]
Dransfield et al	FF/Vil 100/25 vs Vil 25	52 weeks	0.81	1.11	30*
Anzueto et al	FP/Salm 500/100 vs Salm 100	52 weeks	1.10	1.59	30.4[a]
Ferguson et al	FP/Salm 500/100 vs Salm 100	12 months	1.06	1.53	30.5[a]
Sharafkhaneh et al	BUD/FF 400/12 vs FF 12	12 months	0.70	1.07	34.6[a]
Kardos et al	FP/Salm 1000/100 vs Salm 100	44 weeks	0.92	1.4	35[a]

*[a] p-value ICS/LABA vs. LABA alone <0.05, * p value not available*

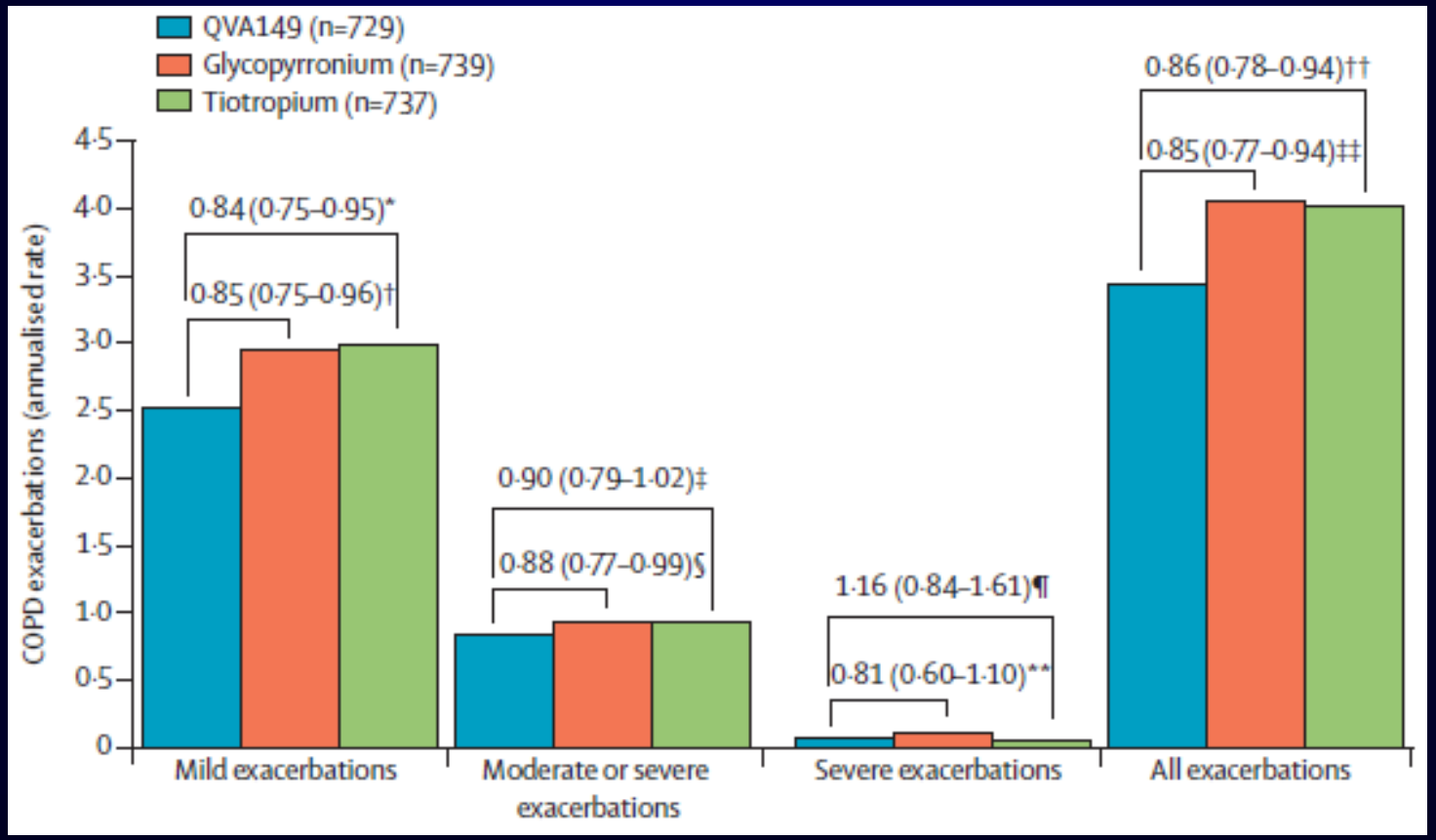
Nannini et al, Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD006829

GOLD 2019



GOLD 2019 Report: Available from http://goldcopd.org/gold-2019-global-strategy-diagnosis-management-prevention-copd

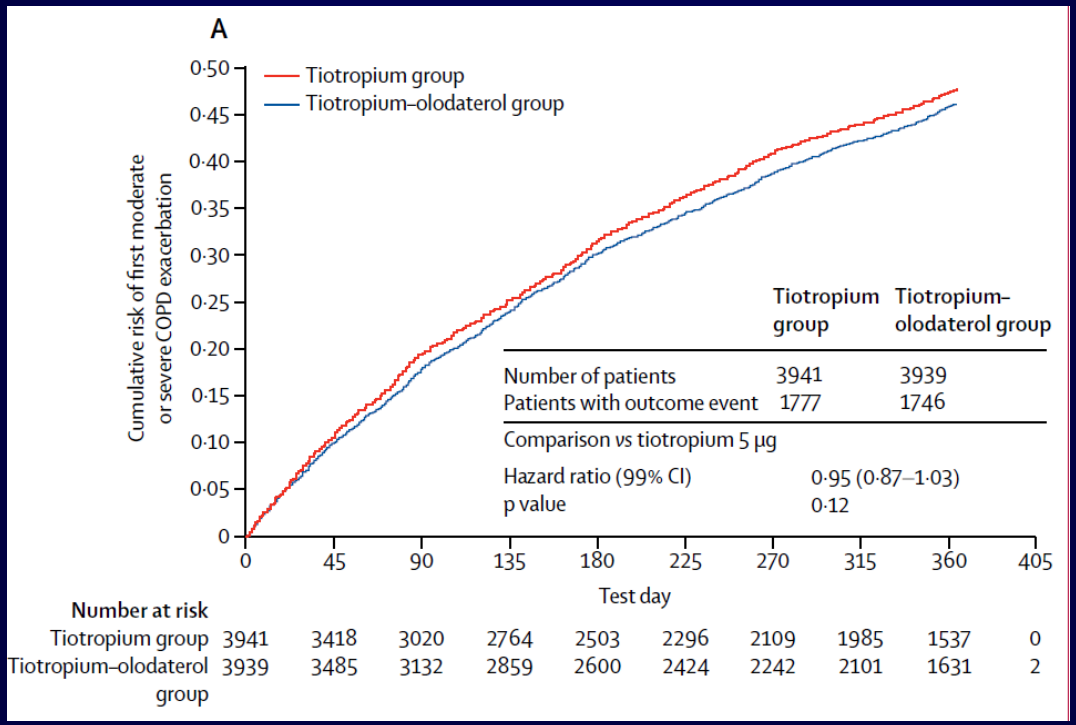
Exacerbations



Wedzicha et al, *Lancet Respir Med* 2013; 1: 199-209

Tiotropium and olodaterol in the prevention of chronic obstructive pulmonary disease exacerbations (DYNAGITO): a double-blind, randomised, parallel-group, active-controlled trial

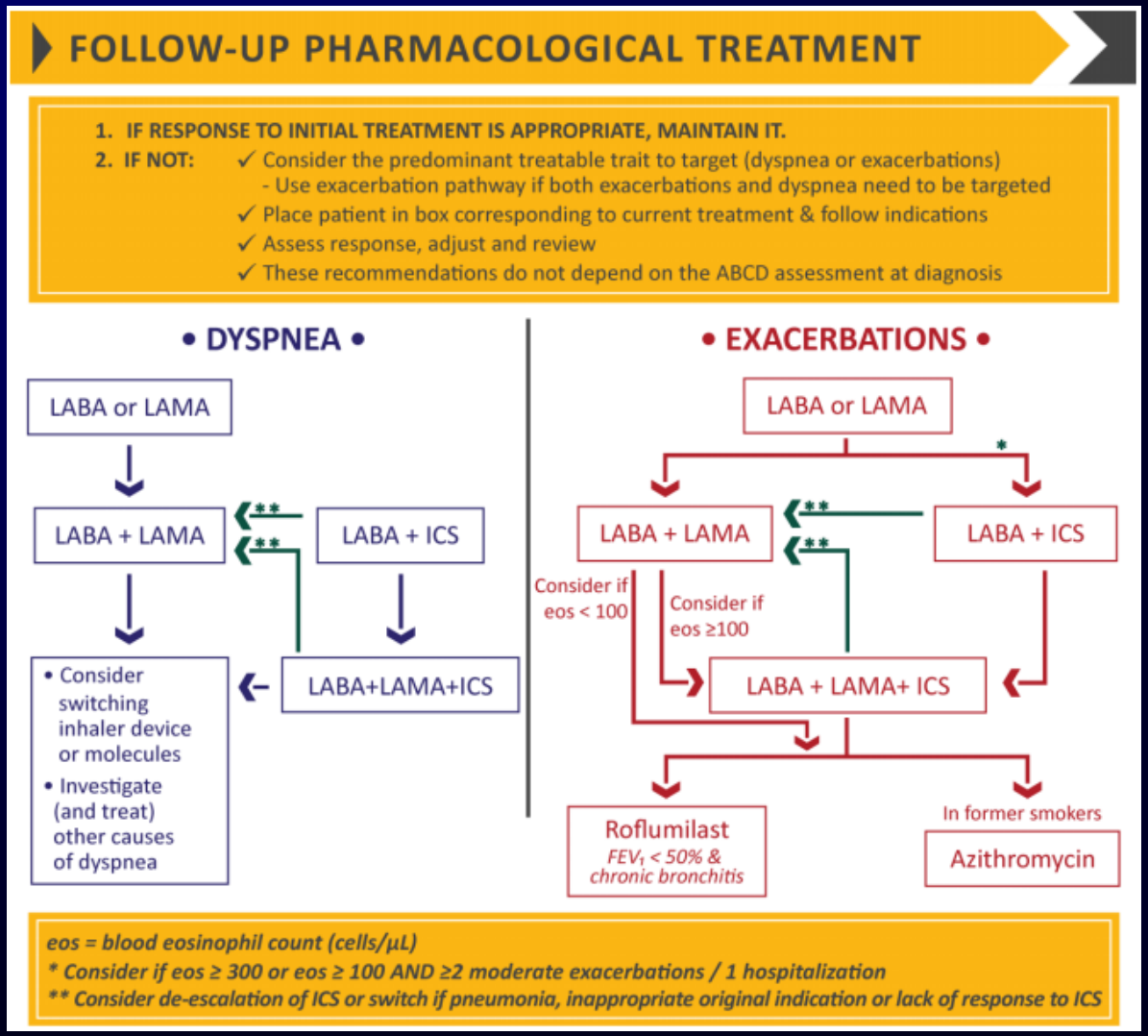
Peter M A Calverley, Antonio R Anzueto, Kerstine Carter, Lars Grönke, Christoph Hallmann, Christine Jenkins, Jadwiga Wedzicha, Klaus F Rabe



The rate of moderate and severe exacerbations was lower with tiotropium–olodaterol than tiotropium (rate ratio [RR] 0.93, 99% CI 0.85–1.02;p=0.0498), not meeting the targeted 0.01 significance level.

Calverley et al., Lancet Respir Med 2018; 6: 337–44

GOLD 2019



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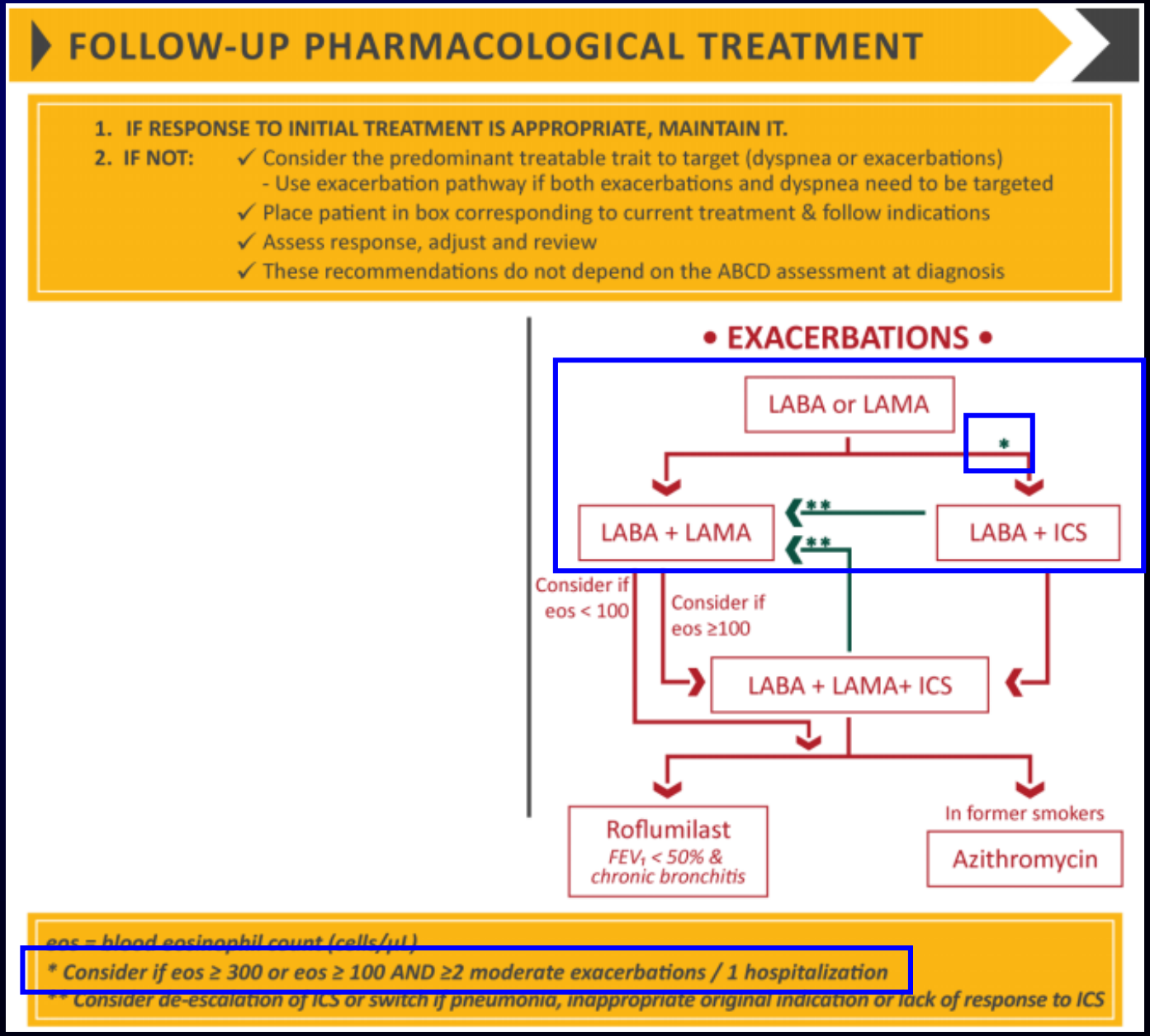
GOLD 2019



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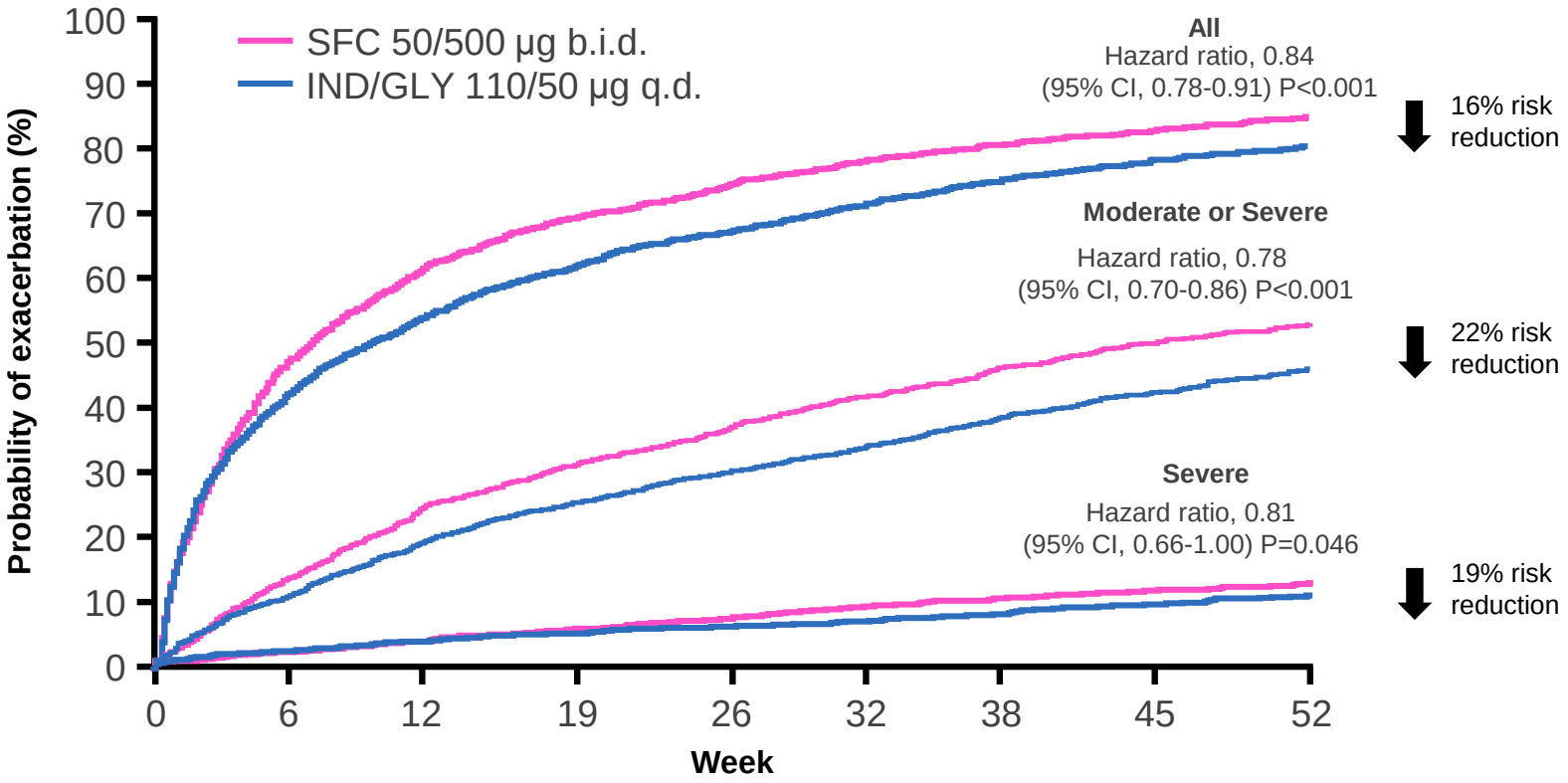
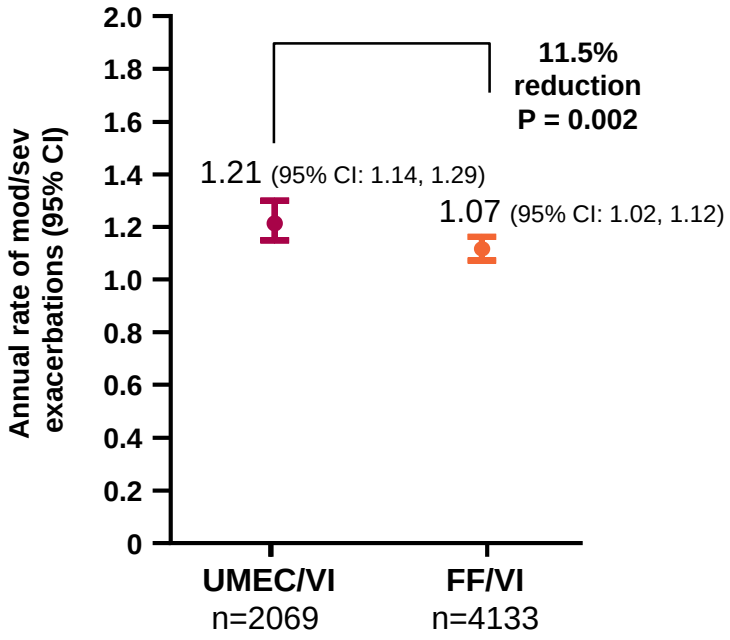
IND/GLY significantly delayed the time to first exacerbation compared with F/SALM



Wedzicha JA, et al.NEJM2016, Online May 15, 2016. DOI: 10.1056/NEJMoa1516385

Analysis of the mITT

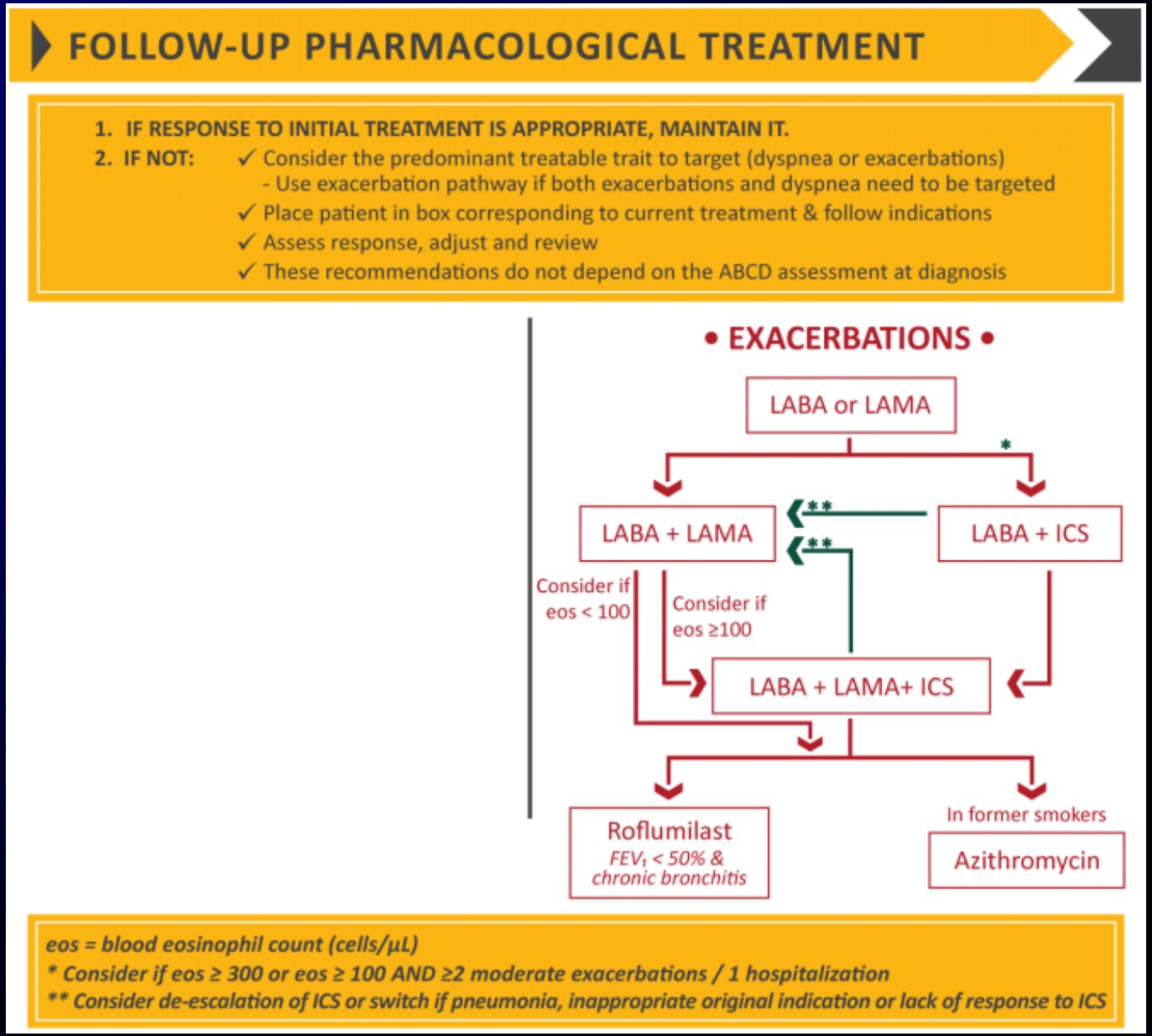
ICS/LABA decreased the rate of on-treatment moderate/ severe exacerbations compared with LAMA/LABA



Note: The n reflects the number of patients included in each analysis from the ITT population. Patients were excluded if they had predefined data missing; this varied according to the analysis. The ITT population comprised: 4151 patients treated with FF/UMEC/VI, 4134 patients treated with FF/VI and 2070 patients treated with UMEC/VI.

Lipson DA, et al. *N Engl J Med*. 2018; 378: 1671-80

GOLD 2019



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  - Triple Therapy: Efficay & Safety
- ….and beyond: new hopes
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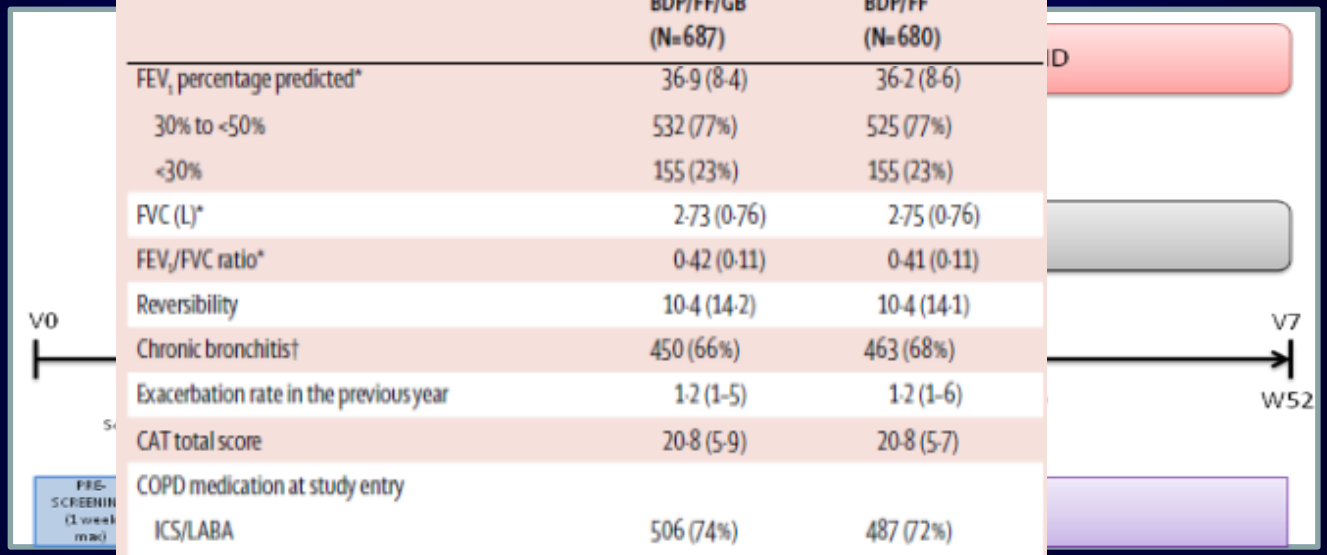
THE LANCET

Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β_2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial

Dave Singh, Alberto Papi, Massimo Corradi, Ilona Pavlišová, Isabella Montagna, Catherine Francisco, Géraldine Cohuet, Stefano Vezzoli, Mario Scuri, Jørgen Vestbo

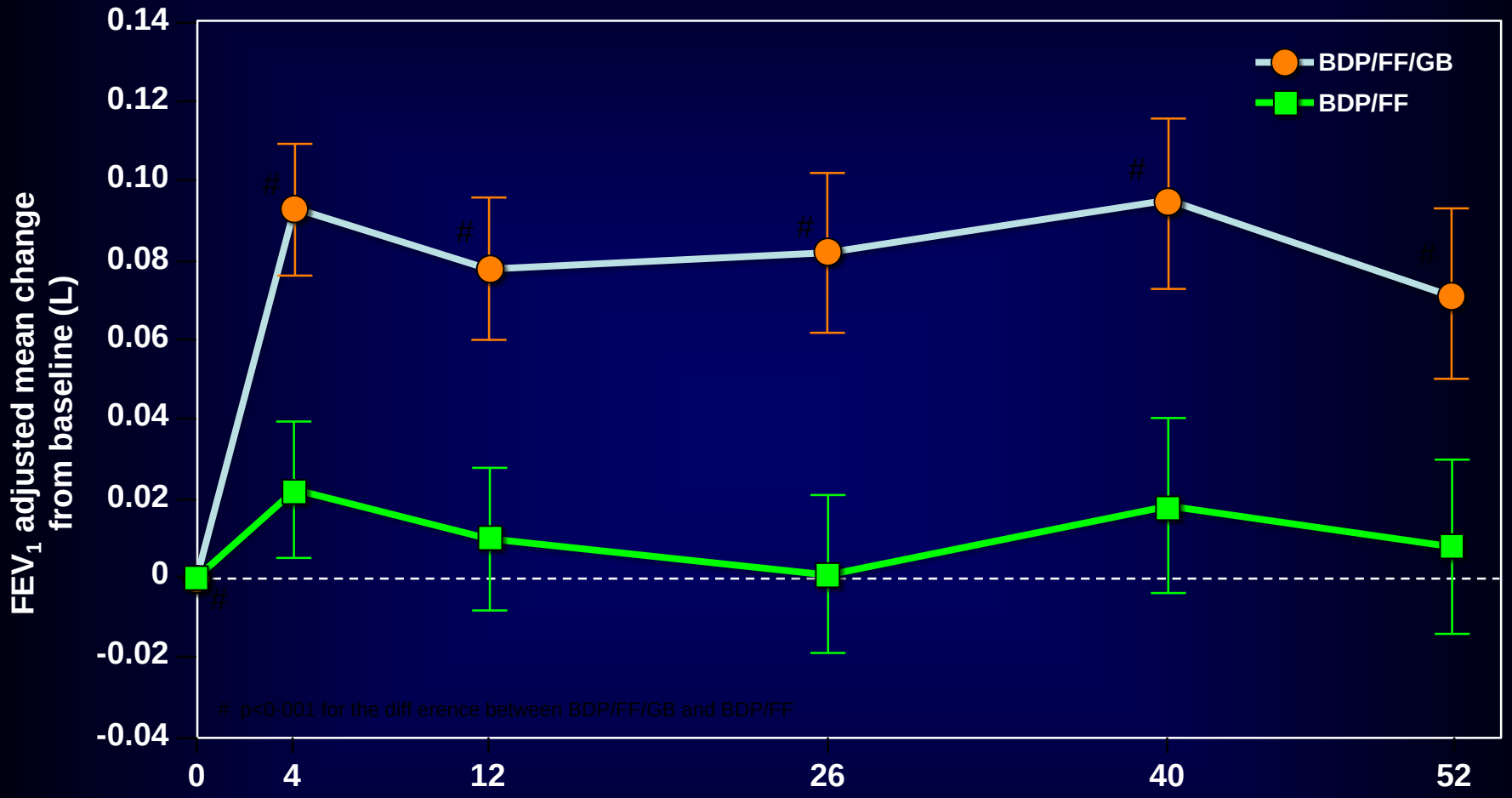
Double-blind, randomized, multinational, multicentre, 2-arm parallel-group, active-controlled study



	BDP/FF/GB (N=687)	BDP/FF (N=680)
FEV$_1$ percentage predicted*	36·9 (8·4)	36·2 (8·6)
30% to <50%	532 (77%)	525 (77%)
<30%	155 (23%)	155 (23%)
FVC (L)*	2·73 (0·76)	2·75 (0·76)
FEV$_1$/FVC ratio*	0·42 (0·11)	0·41 (0·11)
Reversibility	10·4 (14·2)	10·4 (14·1)
Chronic bronchitis†	450 (66%)	463 (68%)
Exacerbation rate in the previous year	1·2 (1–5)	1·2 (1–6)
CAT total score	20·8 (5·9)	20·8 (5·7)
COPD medication at study entry		
ICS/LABA	506 (74%)	487 (72%)
ICS/LAMA	10 (1%)	10 (1%)
LABA/LAMA	95 (14%)	107 (16%)
LAMA	76 (11%)	76 (11%)
Spacer use during the study	111 (16%)	129 (19%)

Singh D, Papi A et al., Lancet 2016

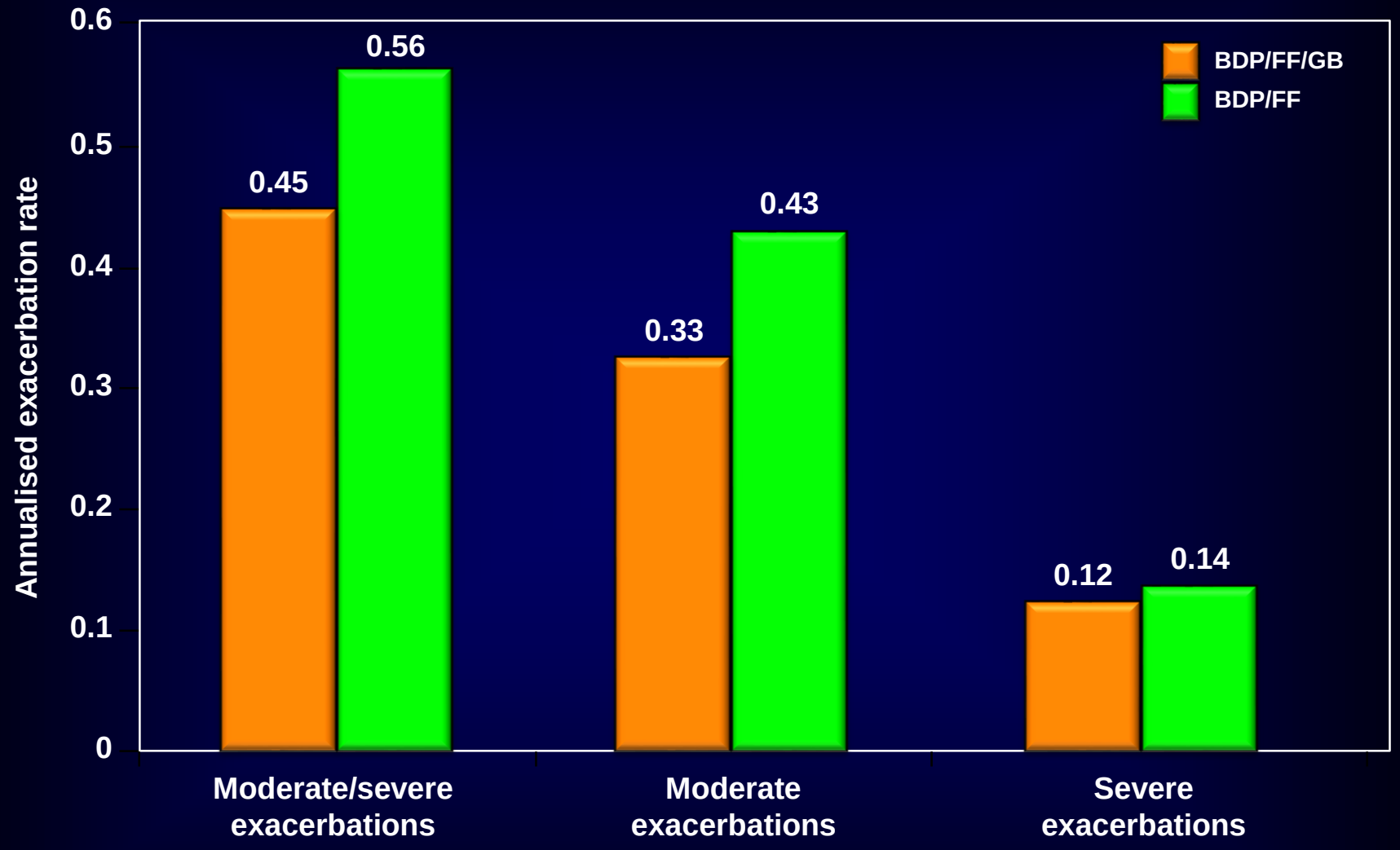
ADJUSTED MEAN CHANGE FROM BASELINE FOR PRE-DOSE FEV_1



N. with available measurements						
BDP/FF/GB	686	679	660	642	622	606
BDP/FF	679	679	654	616	597	578

Singh D. et al., Lancet 2016; 388: 963–73

UNADJUSTED ANNUAL RATE OF COPD EXACERBATIONS OF DIFFERENT SEVERITIES



Singh D. et al., Lancet 2016; 388: 963–73

TRILOGY KEY RESULTS

TRILOGY study provides for the first time one-year evidence that:

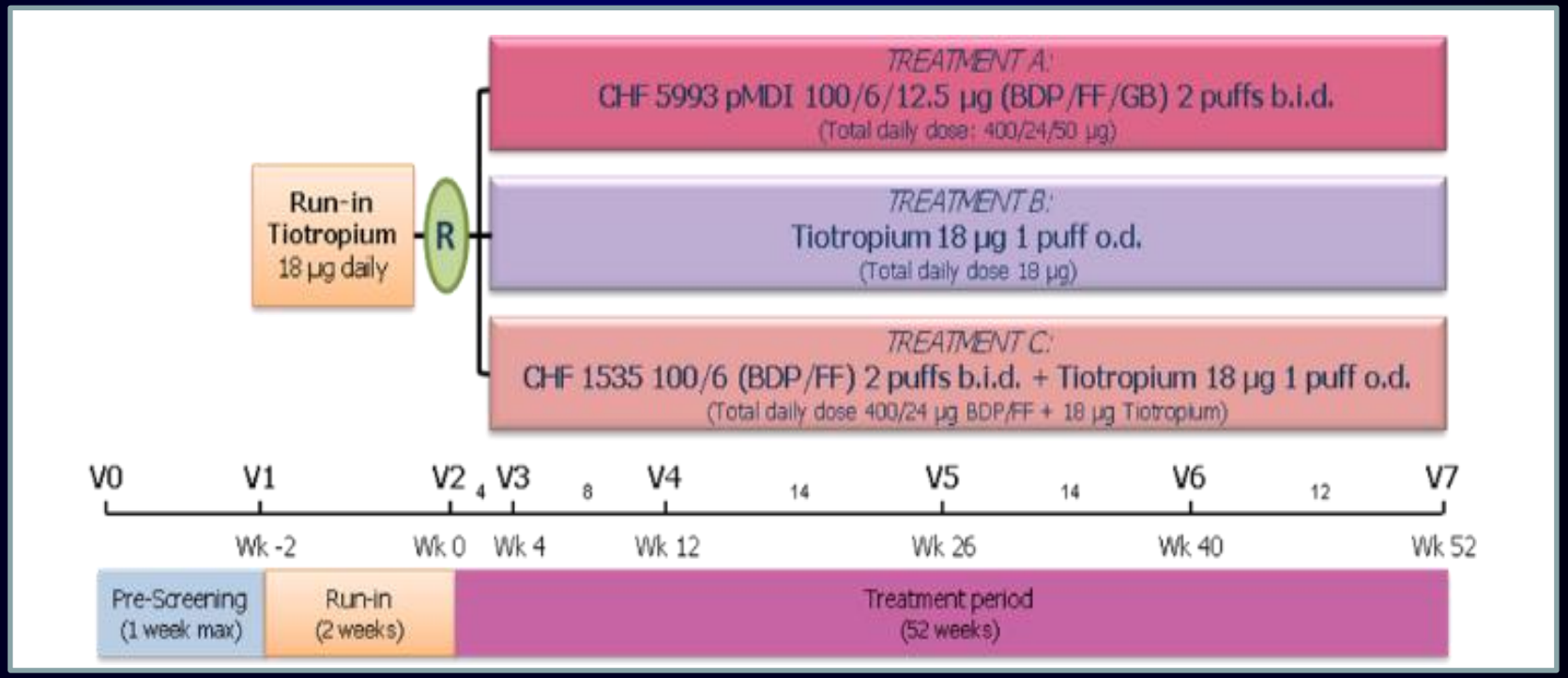
- BDP/FF/GB is superior vs ICS/LABA in terms of pre-dose morning FEV1 and 2-hour post-dose FEV1
- BDP/FF/GB significantly reduced moderate/severe exacerbation rate vs ICA/LABA
- Both treatments led to a clinically significant improvement of TDI. With BDP/FF/GB a significantly greater percentage of responders was observed at week 26
- Other symptoms-based and lung function parameters (SGRQ and Exact-RS scores, FVC) consistently supported the superior clinical efficacy of BDP/FF/GB
- BDP/FF/GB is well tolerated

Singh D, Papi A, et al., Lancet 2016; 388: 963–73

Triple 6 (TRINITY) – Study Design/ Treatments

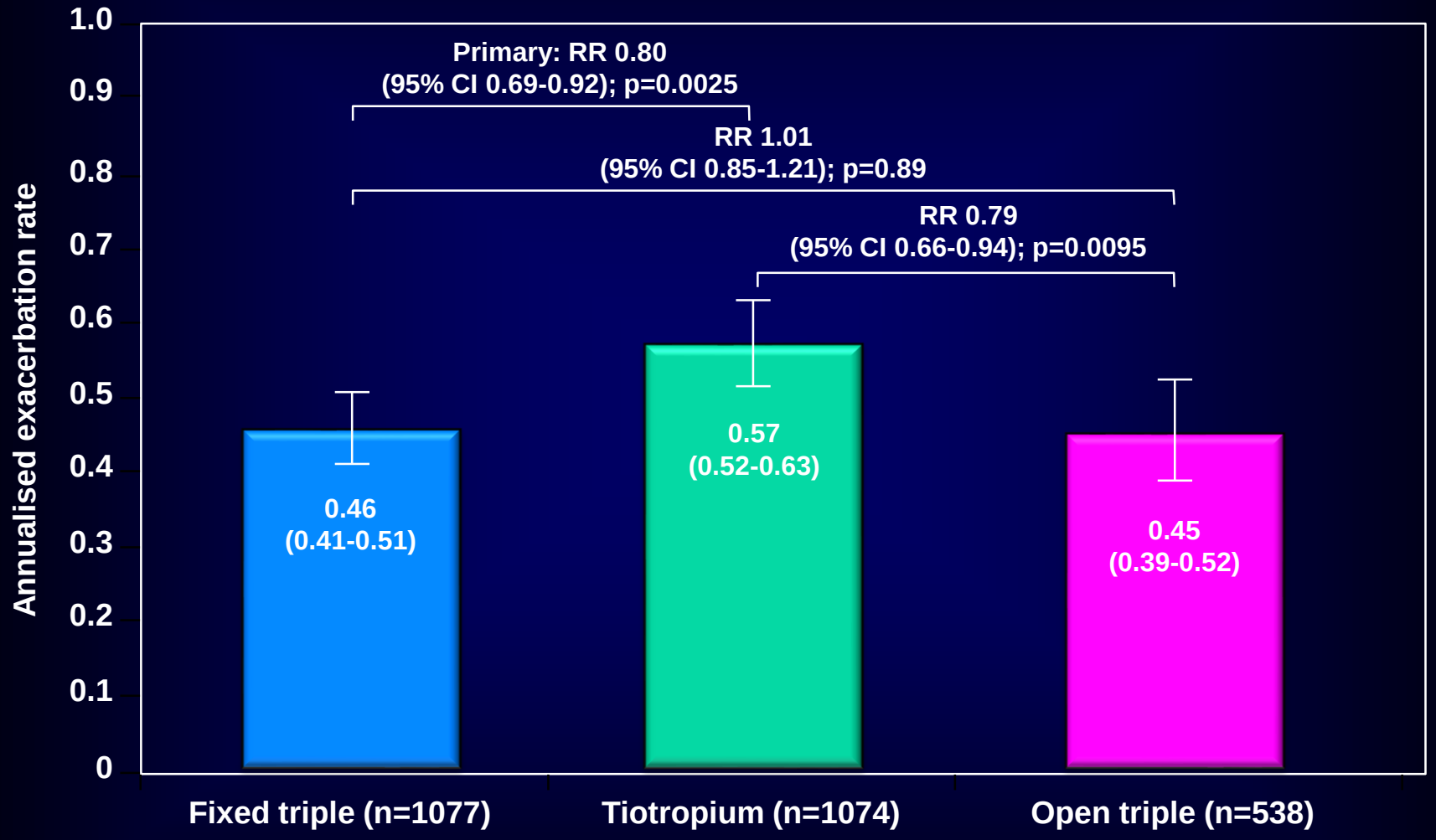
THE LANCET

Double-blind, double-dummy, randomized, multinational, multicentre, 3-arm parallel-group, active-controlled study



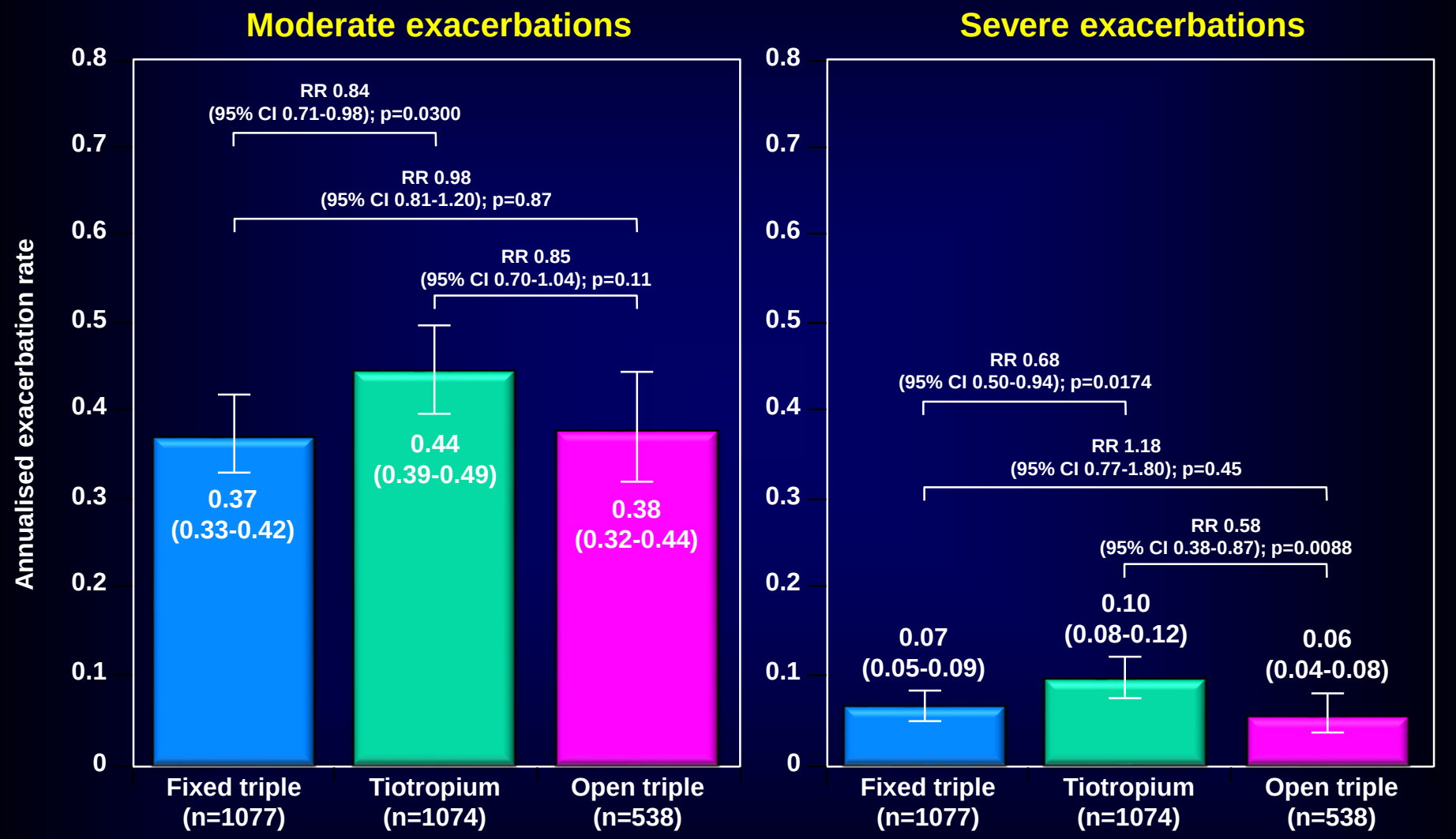
Vestbo J , Papi A et al., Lancet 2017; 389: 1919–29

ADJUSTED ANNUAL RATE OF MODERATE TO-SEVERE COPD EXACERBATIONS



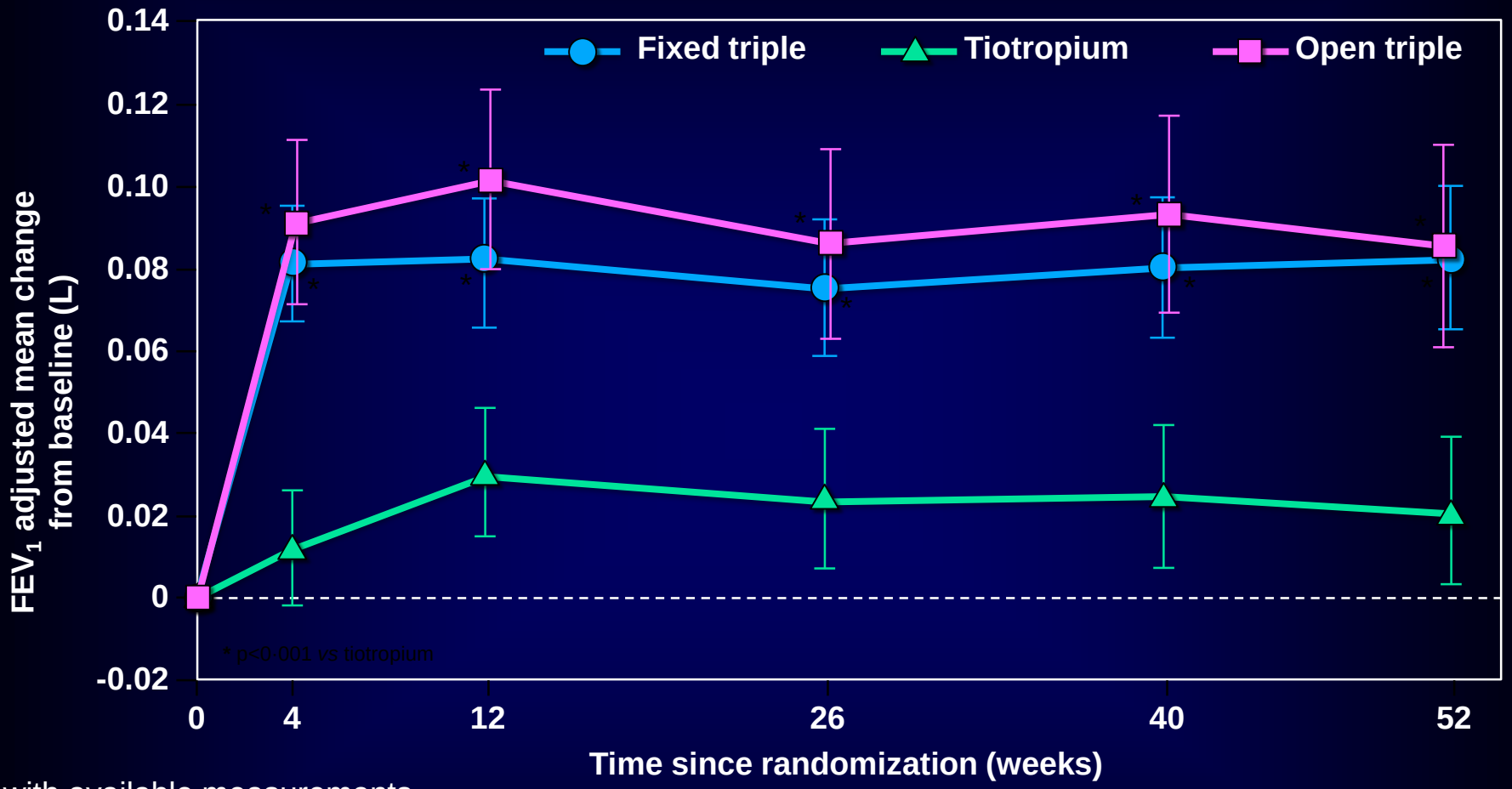
Vestbo J. et al., Lancet 2017; 389: 1919–29

ADJUSTED ANNUAL RATE OF SEVERE AND MODERATE COPD EXACERBATIONS



Vestbo J. et al., Lancet 2017; 389: 1919–29

ADJUSTED MEAN CHANGE FROM BASELINE IN PREDOSE FEV_1



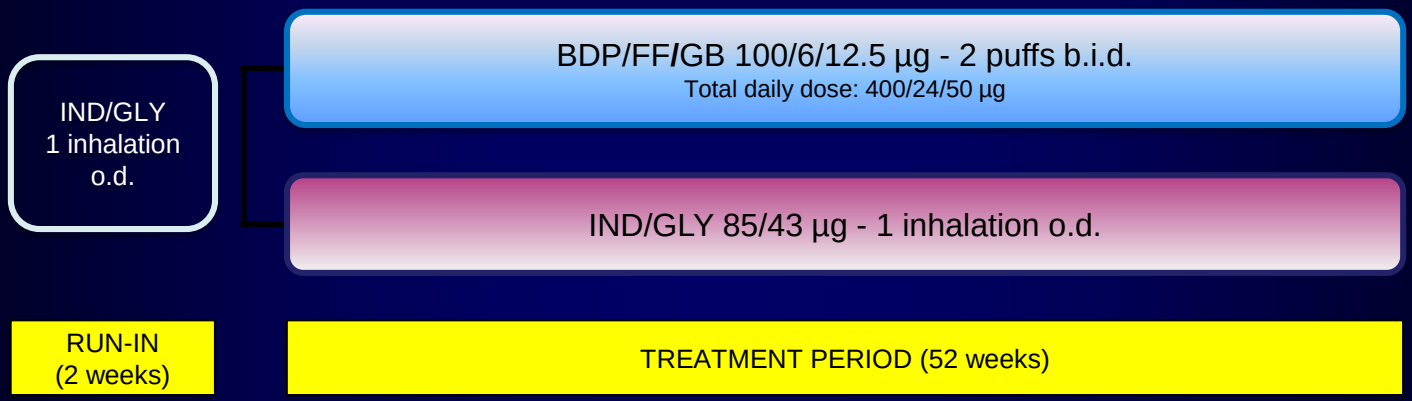
N. with available measurements

Fixed triple	1077	1067	1047	1027	998	985
Tiotropium	1074	1052	1019	977	944	921
Open triple	538	536	526	510	502	495

Vestbo J. et al., Lancet 2017; 389: 1919–29

Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial

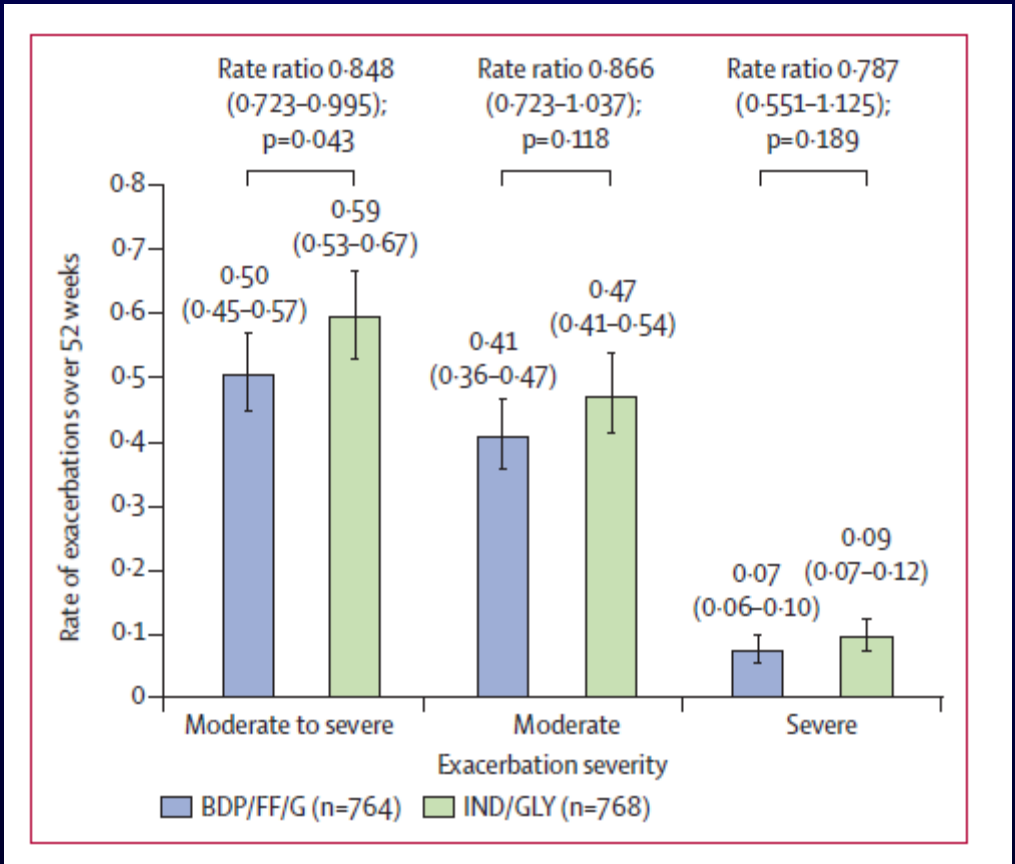
Alberto Papi, Jørgen Vestbo, Leonardo Fabbri, Massimo Corradi, Hélène Prunier, Géraldine Cohuet, Alessandro Guasconi, Isabella Montagna, Stefano Vezzoli, Stefano Petruzzelli, Mario Scuri, Nicolas Roche, Dave Singh**



- Same population as TRILOGY and TRINITY
- Blinded
- Aim: to demonstrate superiority of ICS/LABA/LAMA vs LABA/LAMA combination
- Primary Endpoint : exacerbations

Papi A, Vestbo J, et al The Lancet, 2018

Moderate/severe COPD exacerbation rate (ITT)

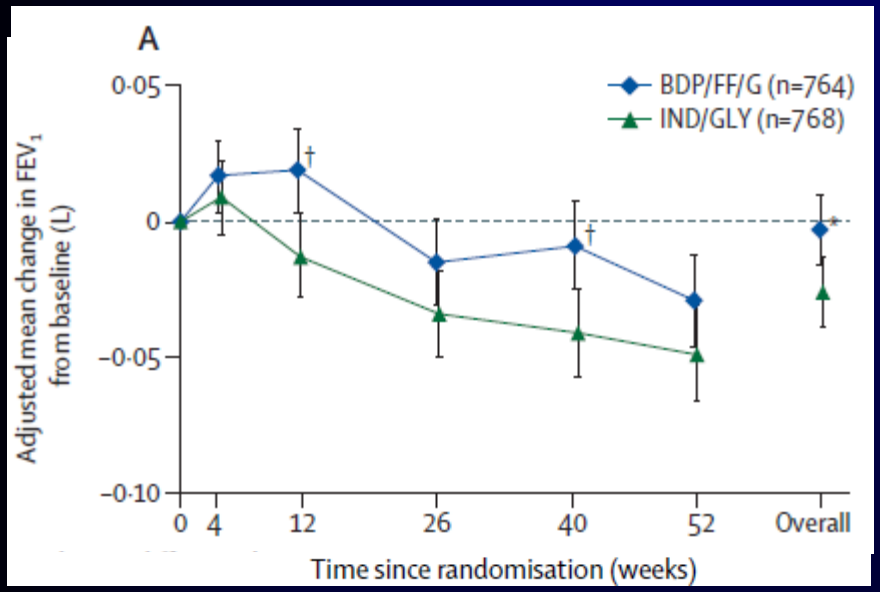


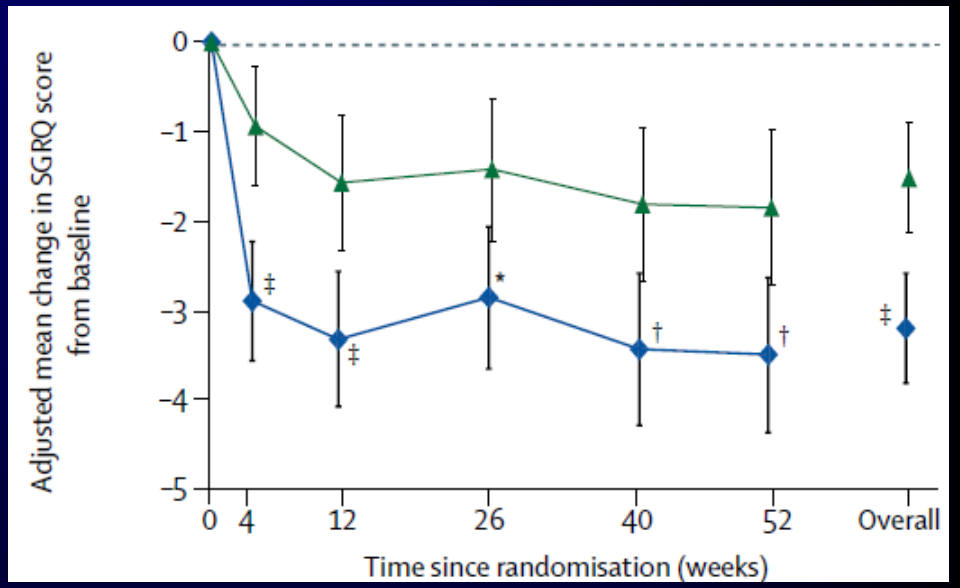
Primary endpoint met. Superiority demonstrated.

A **15.2% reduction** of moderate/severe COPD exacerbations is found for BDP/FF/GB pMDI compared to IND/GLY

Papi A, Vestbo J, et al Lancet 2018

TRIBUTE

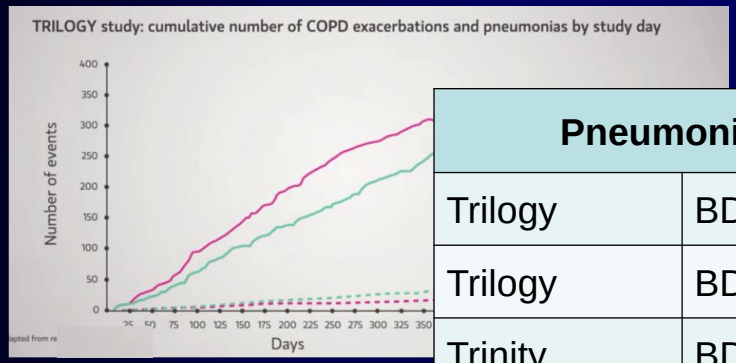




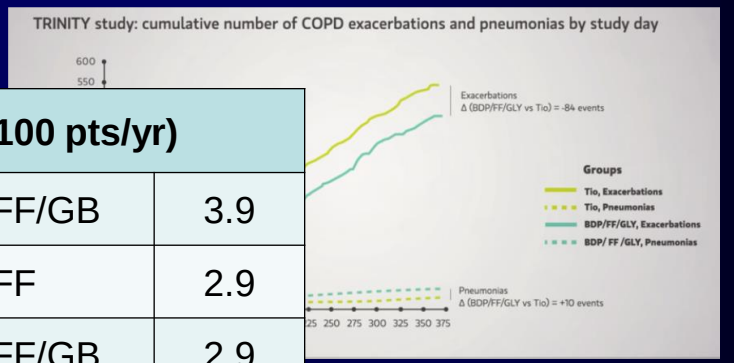
Papi A et al. Lancet 2018; 391: 1076–84

Risk-benefit ratio (COPD exacerbations and pneumonias) in Trilogy, Trinity and Tribute studies

TRILOGY

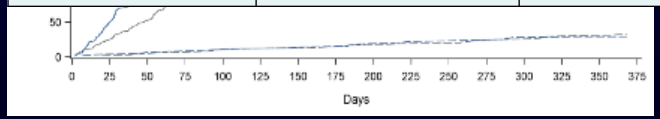


TRINITY



Pneumonia (100 pts/yr)		
Trilogy	BDP/FF/GB	3.9
Trilogy	BDP/FF	2.9
Trinity	BDP/FF/GB	2.9
Trinity	Tiotropium	1.9
Trinity	BDP/FF +TIO	2.5
Tribute	Inda/Glyco	4.4
Tribute	BDP/FF/GB	4.1

TRIBUTE



Singh D et al., Lancet 2016; Vestbo J et al., Lancet 2017; Papi A et al., Lancet 2018

EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has reviewed the risk of pneumonia with inhaled corticosteroid-containing medicines when used to treat COPD.

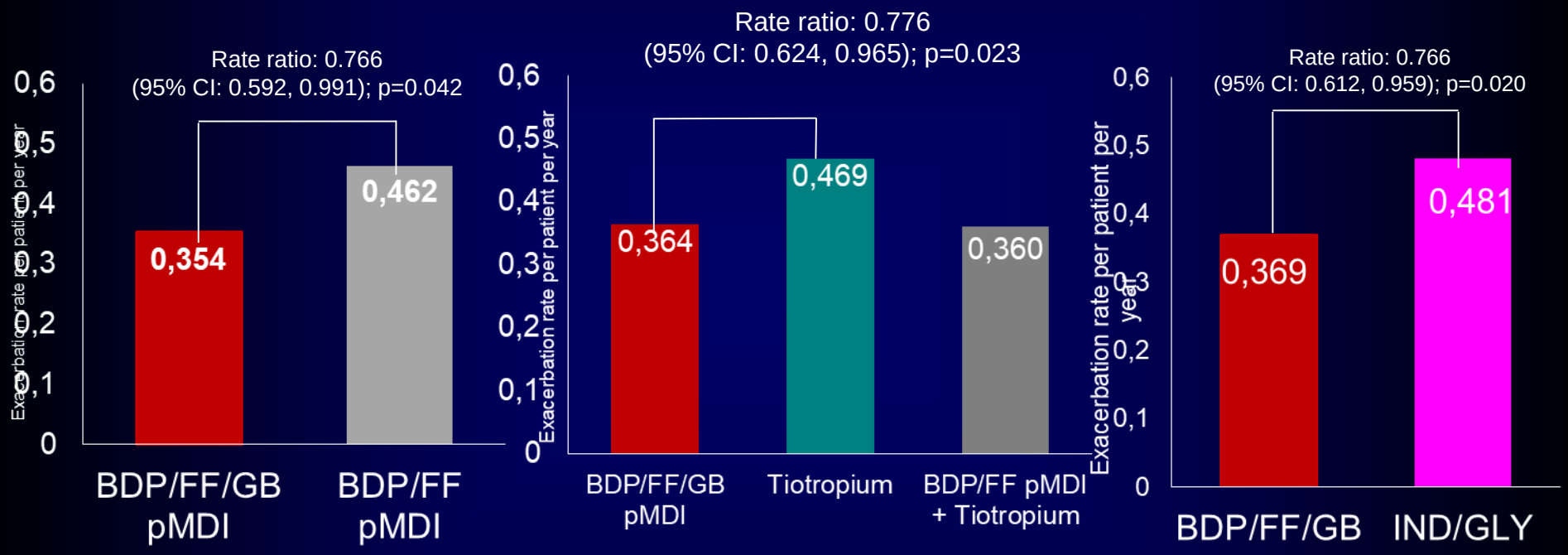
The PRAC review confirms that COPD patients treated with inhaled corticosteroids are at increased risk of pneumonia; however the Committee's view is that the benefits of inhaled corticosteroids continue to outweigh their risks

14/07/2016 EMA/488280/2016

Triple therapies: opening spaces for hope in COPD patients

- Definitions & treatment outcomes.
- Exacerbations and their prevention
  - GOLD 2019-20
- New options, space for hopes
  - Triple Therapy: Efficay & Safety
- ….and beyond: new hopes

Moderate/severe COPD exacerbation rate in patients with 1 moderate exacerbation in the previous year



TRILOGY

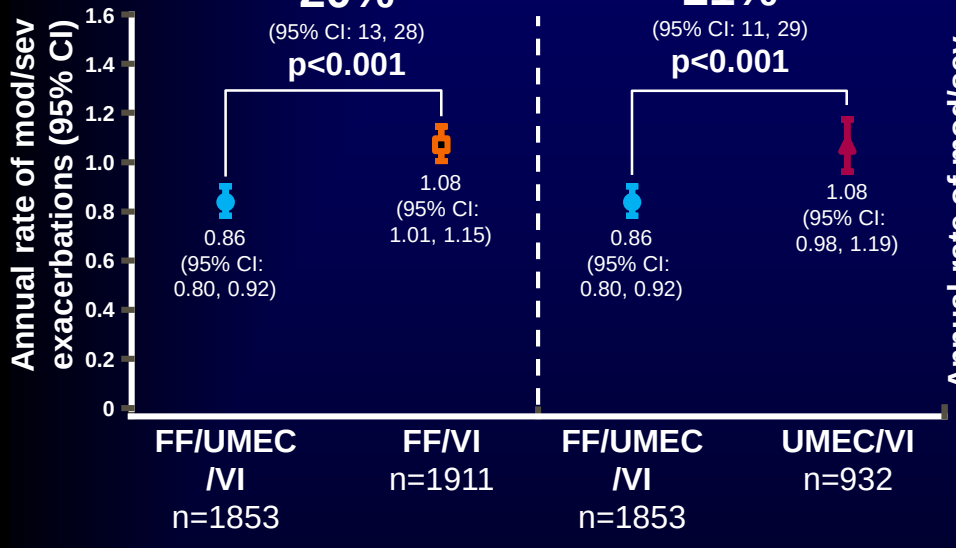
TRINITY

TRIBUTE

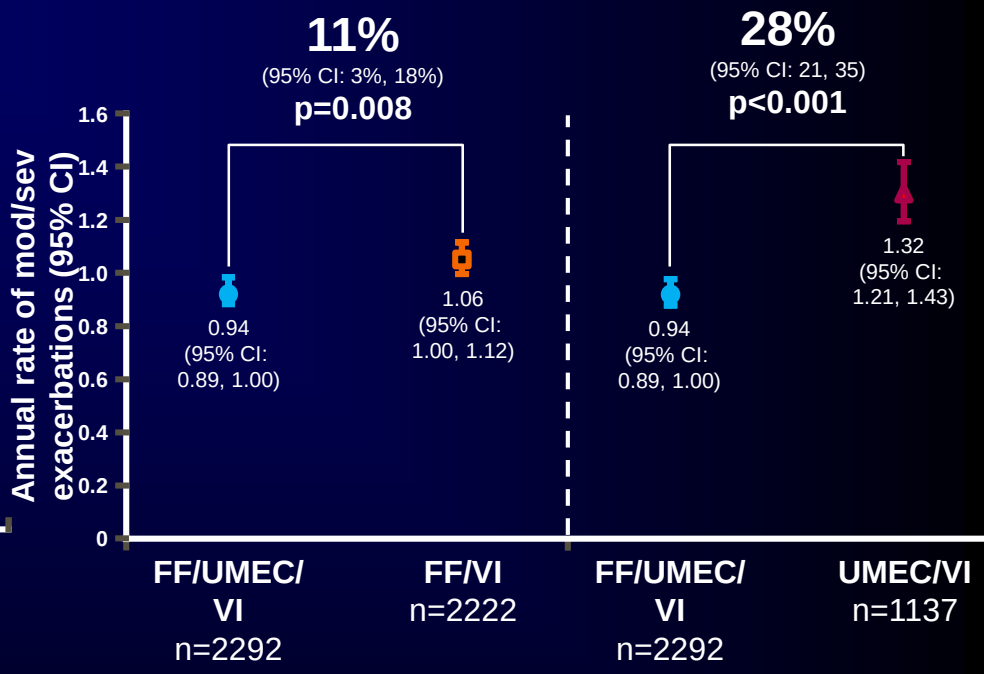
Singh et al., Eur Resp J 2019; 53: 1900235

Moderate/severe exacerbations in patients experiencing

1 moderate/severe exacerbation in the last 12 months

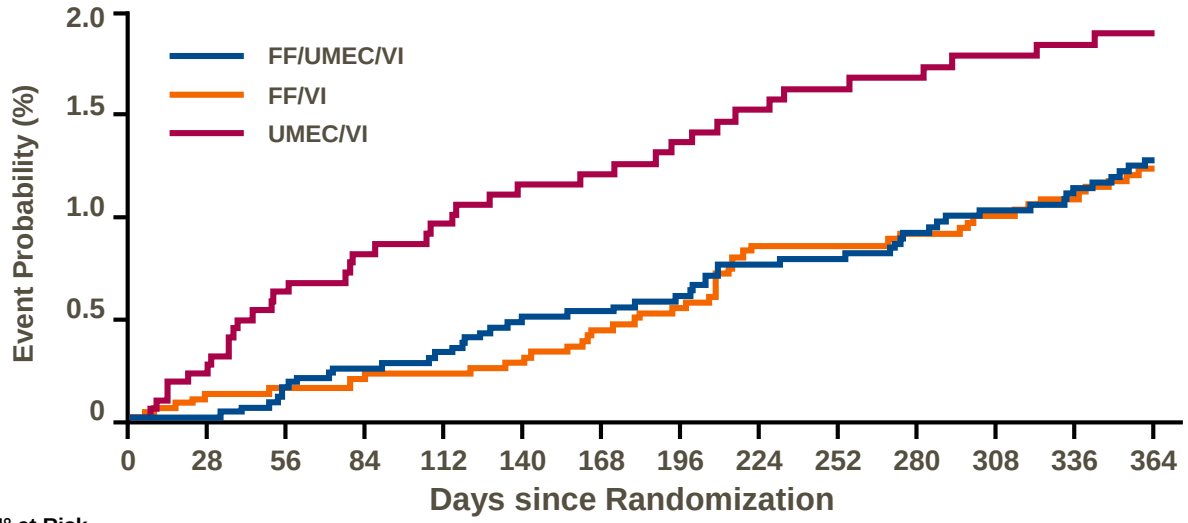


≥ 2 moderate/severe exacerbation in the last 12 months



Lipson DA et al. NEJM 2018

IMPACT MORTALITY (data on-treatment)



N° at Risk

FF/UMEC/VI	4151	4082	3968	3898	3838	3752	3714	3690	3613	3581	3545	3486	3454	3346
FF/VI	4134	3984	3798	3694	3619	3496	3443	3391	3291	3258	3230	3182	3152	3044
UMEC/VI	2070	1993	1880	1820	1769	1713	1685	1656	1612	1595	1578	1548	1531	1485

FF/UMEC/VI vs UMEC/VI

42.1%

HR 0.58
(95% CI: 0.38, 0.88)
p=0.011

FF/VI vs UMEC/VI

38.7%

HR 0.61
(95% CI: 0.40, 0.93)
p=0.022

Lipson DA et al NEJM 2018

ICS containing combinations and Mortality in COPD

Eur Respir J. 2018 Dec 13;52(6). pii: 1801230

Table 1. Patients (%) with fatal AEs and Hazard Ratios for the treatment group comparisons in TRILOGY, TRINITY and TRIBUTE

Study	Test	Comparator	Number of patients with event (%) - Test	Number of patients with event (%) - Comparator	Hazard Ratio (95% CI), p-value
Single					
TRILOGY	BDP/FF/G (N=687)	BDP/FF (N=680)	15 (2.2%)	16 (2.4%)	-
TRINITY	BDP/FF/G (N=1077)	TIO (N=1076)	20 (1.9%)	29 (2.7%)	-
	'	BDP/FF+TIO (537)	'	8 (1.5%)	-
TRIBUTE	BDP/FF/G (N=764)	IND/GLY (N=768)	16 (2.1%)	21 (2.7%)	
Pooled					
TRILOGY, TRINITY, TRIBUTE	BDP/FF/G, BDP/FF, BDP/FF+TIO (N=3745)	TIO, IND/GLY (N=1844)	75 (2.0%)	50 (2.7%)	0.72 (0.50; 1.02), p=0.066
	BDP/FF/G (N=2528)	TIO, IND/GLY (N=1844)	51 (2.0%)	50 (2.7%)	0.72 (0.49; 1.06), p=0.096

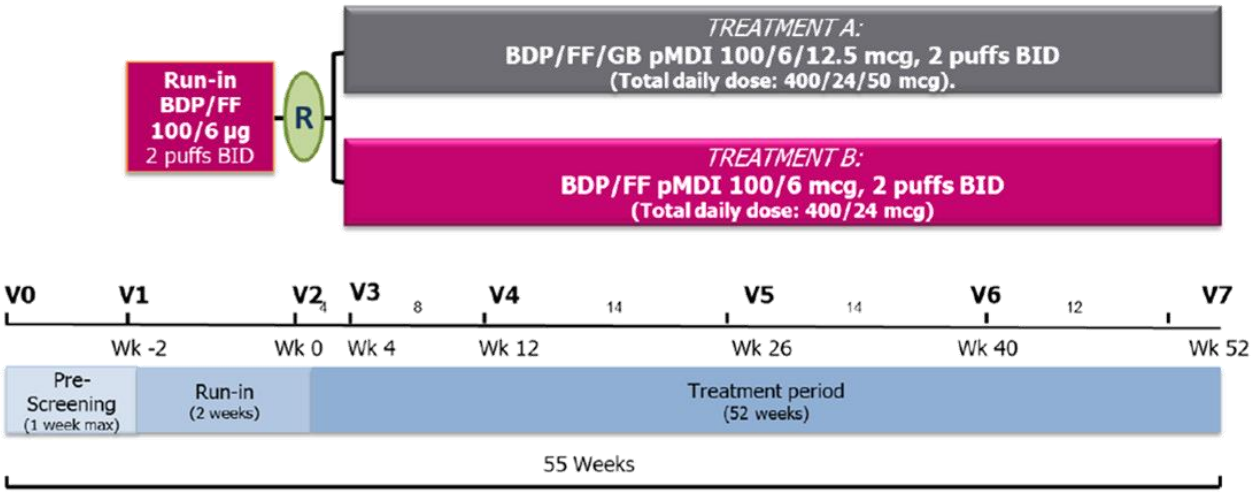
	BDP/FF/G, BDP/FF, BDP/FF+TIO (n=3745)	TIO, IND/GLY (N=1844)	
	N of patients with events (%)		HR (95%, CI), p-value
RESPIRATORY	19 (0.5%)	9 (0.5%)	1.01 (0.45; 2.22) p=0.990
NON-RESPIRATORY	56 (1.5%)	41 (2.2%)	0.65 (0.43; 0.97) p=0.037

Vestbo J, Fabbri L, Papi A, Petruzzelli S, Scuri M, Guasconi A, Vezzoli S, Singh D. Eur Resp J 2018

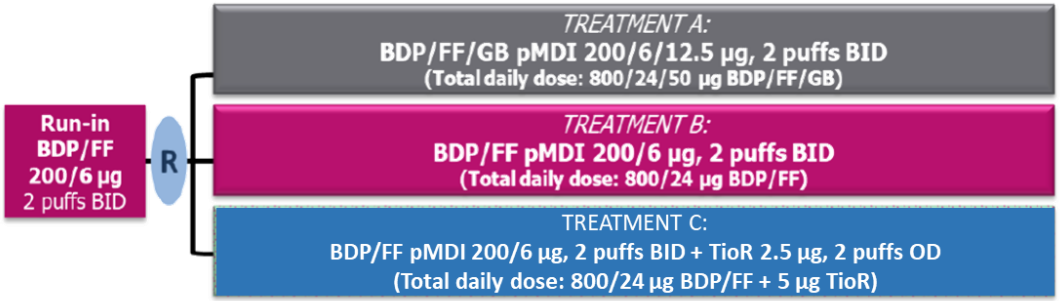
GOLD 2020 Triple therapy. Mortality

- Recently, trials utilizing triple combinations of LABA/LAMA/ICS in comparison to LAMA, LABA/LAMA or LABA/ICS have reported reduced mortality with triple therapy. (Lipson NEJM 2018; Vestbo ERJ 2019). Unlike previous trials, the recent studies target patient populations that are enriched for increased respiratory symptoms and a prior history of frequent and/or severe exacerbations with the majority receiving background treatment with triple or LABA/ICS based therapy before study enrollment.
- The largest of these trials (n=10,355) compared single inhaler triple therapy versus ICS/LABA or LABA/LAMA dual therapy; there was a statistically significant 42.1% reduction in the risk of on-treatment allcause mortality and a 28.6% reduction in the risk of all-cause mortality including off-treatment data, comparing triple therapy with LABA/LAMA (Lipson NEJM 2018)
- A *post-hoc* pooled analysis of triple therapy clinical trials conducted in severe COPD patients with a history of exacerbations showed a trend for lower mortality with use of triple inhaled therapy compared to non-ICS based treatments, but the differences were not statistically significant. (Vestbo ERJ 2019).
- *It should be noted that none of the recent studies reporting a reduction in mortality with triple inhaled therapy had survival as the primary oucome*.

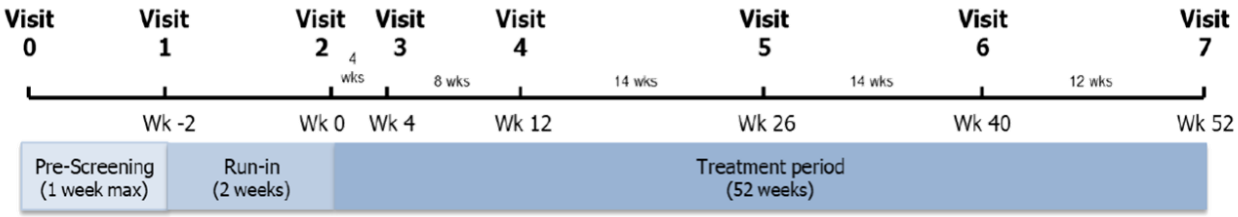
TRIMARAN and TRIGGER: studies design



TRIMARAN study



TRIGGER study



Data not yet submitted to EMA
BDP/FF/GB is not indicated in asthmatic patients

Virchow JC, Kuna P, Paggiaro P, Papi A, Singh D, Corre S, Zuccaro F, Vele A, Kots M, Georges G, Petruzzelli S, Canonica GW. Lancet, October 1 2019

TRIMARAN and TRIGGER: studies objectives

Primary objectives in each study:

- To demonstrate superiority of BDP/FF/G over BDP/FF in terms of pre-dose FEV_1 at Week 26;
- To demonstrate superiority of BDP/FF/G over BDP/FF in reducing the rate of moderate to severe exacerbations over 52 weeks.

Secondary objectives:

- To demonstrate superiority of BDP/FF/G over BDP/FF in terms of peak FEV_1 at Week 26 and average morning PEF over the first 26 weeks of treatment in each study;
- To demonstrate superiority of BDP/FF/G over BDP/FF in reducing the rate of severe exacerbations using data pooled from the two studies.

Data not yet submitted to EMA
BDP/FF/GB is not indicated in asthmatic patients

Virchow JC, Kuna P, Paggiaro P, Papi A, Singh D, Corre S, Zuccaro F, Vele A, Kots M, Georges G, Petruzzelli S, Canonica GW. Lancet, October 1 2019

TRIMARAN and TRIGGER: results

In TRIMARAN study both **co-primary endpoints were met**:

- At week 26, trough FEV_1 was 57mL higher with BDP/FF/GB than BDP/FF;
- Over the 52 weeks, a 15.4% reduction in the rate of moderate and severe asthma exacerbations was observed in favour of BDP/FF/GB;
- Differences in FEV_1 $Peak_{0-3}$ and morning PEF at week 26 were also observed in favour of BDP/FF/GB.

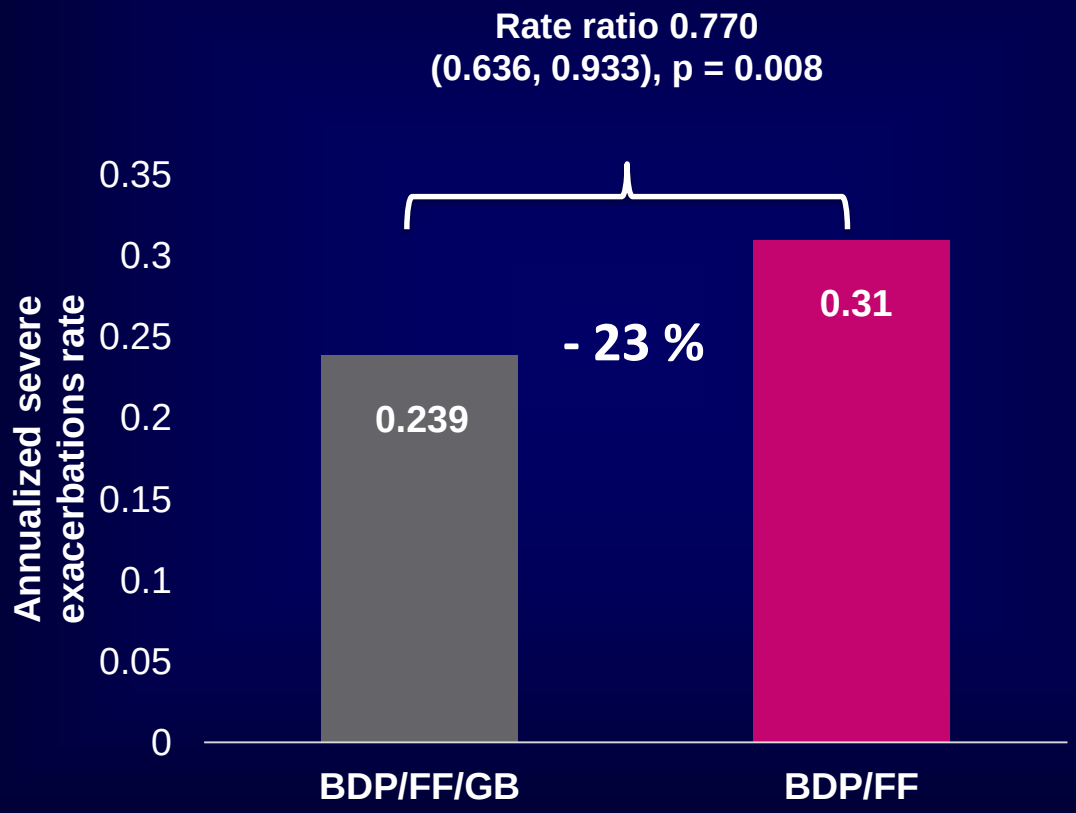
In TRIGGER study:

- Pre-dose FEV_1 at week 26 showed a 73 mL increase in favour of BDP/FF/GB (p=0.003);
- Over the 52 weeks, treatment with BDP/FF/GB resulted in a 12% reduction in the annual rate of moderate and severe asthma exacerbations compared to BDP/FF (RR: 0.880; p=0.110);
- Differences in FEV_1 $Peak_{0-3}$ and morning PEF at week 26 were also observed in favour of BDP/FF/GB.

Data not yet submitted to EMA
BDP/FF/GB is not indicated in asthmatic patients

Virchow JC, Kuna P, Paggiaro P, Papi A, Singh D, Corre S, Zuccaro F, Vele A, Kots M, Georges G, Petruzzelli S, Canonica GW. Lancet, October 1 2019

TRIMARAN and TRIGGER – Results of Pooled prespecified analysis



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Virchow JC, Kuna P, Paggiaro P, Papi A, Singh D, Corre S, Zuccaro F, Vele A, Kots M, Georges G, Petruzzelli S, Canonica GW. Lancet, October 1 2019

Triple therapies: opening spaces for hope in COPD patients

- Definitions & treatment outcomes.
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- New options, new hopes
  - Triple Therapy: Efficay safety
- ….and beyond: new hopes
- In addition….. Letters..

Triple therapy trials in COPD: a precision medicine opportunity

Conclusions

We demonstrated that the timing of the exacerbations in these trials presents a particularly informative pattern. It shows that the lower rate of a first exacerbation with triple therapy is exclusively due to a lower rate in the first month of follow-up. This pattern of "depletion of susceptibles" suggests that there is a subset of patients who could benefit from triple therapy.

We submit that the history of asthma and the prior use of ICS, withdrawn at randomisation, could be two important factors of interest in identifying such subsets of responders

Suissa S, Ariel A. Eur Respir J 2019

Making Sense of Triple Inhaled Therapy for COPD

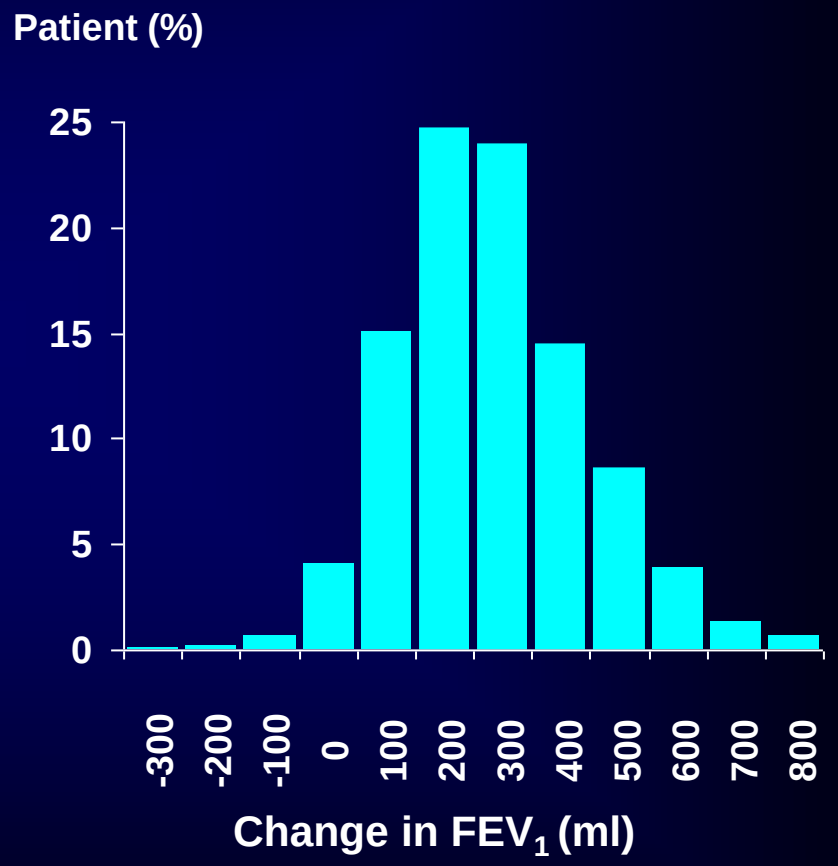
- «…….and patients with a history of asthma were included.

- IMPACT: Subjects meeting any of the following criteria must not be enrolled in the study:….2. **Asthma**: Subjects with *a current diagnosis of asthma*.
- TRIBUTE: Key exclusion criteria were *a current diagnosis of asthma* …..
- POET: Exclusion critaria: Significant diseases other than COPD. ..2. Patients *with a diagnosis of asthma*.
- WISDOM: Key exclusion criteria include: …. *a current clinical diagnosis of asthma*;
- TORCH: Exclusion criteria: *Diagnosis of asthma*
- SUMMIT: Key exclusion criteria….*Current diagnosis of asthma* or…

A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease

Key exclusion criteria were a history of asthma, a……

Distribution of Change in FEV_1 Following Inhalation of 400 µg Salbutamol & 80 µg Ipratropium



Tashkin et al. Eur Respir J. 2008;31:742-50.

To the Editor:

Triple therapy for patients with severe, symptomatic COPD at risk of exacerbations

1) time to first

The analysis of Suissa and Ariel was limited to the first event. In a *post-hoc* analysis of TRIBUTE triple therapy not only prolonged the combined estimate of time to exacerbation vs LAMA/LABA (HR] 0.84; 95% CI 0.74, 0.96; p=0.011) but the effect size increased for multiple events, from an HR of 0.90 (0.76, 1.06) for time to first exacerbation, to 0.80 (0.61, 1.04) for time to second, and 0.58 (0.37, 0.90; p=0.014) for time to third.

Papi A,Petruzzelli S,Vezzoli S, Georges G, Fabbri LM. Eur Respir J, 2019, In press.

To the Editor:

Triple therapy for patients with severe, symptomatic COPD at risk of exacerbations

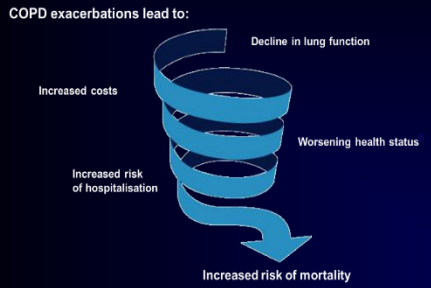
2) History of asthma; 3) ICS withdrawal

History of asthma; Only one patient had a history of asthma; it was therefore not possible to perform analyses stratified by this factor, but intrinsically this rules out the possibility that in TRIBUTE, the observed early effect on exacerbations was due to patients with a history of asthma.
ICS withdrawal….To the contrary, the subgroup that gained most benefit from triple therapy over the duration of the study was that in which patients were not receiving ICS prior to study entry. Over the first four weeks, the initial increase in exacerbation incidence in the LAMA/LABA group occurred in both the prior ICS and no prior ICS subgroups, with patients receiving LAMA/LABA approximately twice as likely to exacerbate than triple in both subgroups

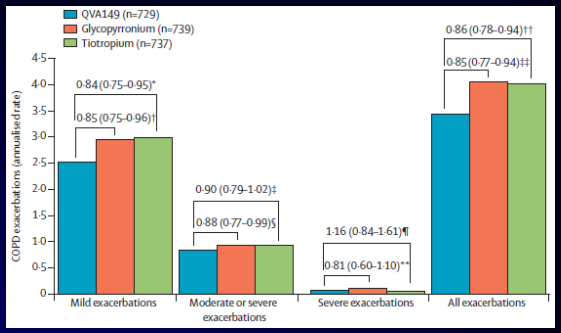
Thus, Suissa and Ariel's speculation about the TRIBUTE results is not supported by evidence.

Papi A, Petruzzelli S,Vezzoli S, Georges G, Fabbri LM. Eur Respir J, 2019, In press.

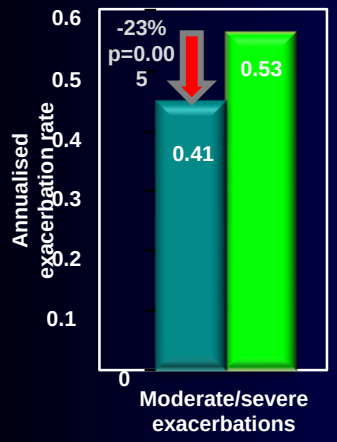
Summary



Study reference	Drugs and total daily dose (µg)	Study duration	Annual rate of moderate/severe exacerbations		
			ICS/LABA	LABA	Reduction ICS/LABA vs LABA (%)
Calverley et al	FP/Salm 1000/100 vs Salm 100	3 years	0.85	0.97	12[a]
Szafranski et al	BUD/FF 800/24 vs FF 24	12 months	1.42	1.84	23[a]
Rennard et al	BUD/FF 400/12 vs FF 12	12 months	n/a	n/a	25[a]
Calverley et al	BUD/FF 800/24 vs FF 24	12 months	1.38	1.85	25.5[a]
Sharafkhaneh et al	BUD/FF 200/12 vs FF 12	12 months	0.79	1.07	25.9[a]
Wedzicha et al	BDP/FF 400/24 vs FF 24	48 weeks	0.80	1.12	28.1[a]
Rennard et al	BUD/FF 200/12 vs FF 12	12 months	n/a	n/a	29[a]
Dransfield et al	FF/Vil 100/25 vs Vil 25	52 weeks	0.81	1.11	30*
Anzueto et al	FP/Salm 500/100 vs Salm 100	52 weeks	1.10	1.59	30.4[a]
Ferguson et al	FP/Salm 500/100 vs Salm 100	12 months	1.06	1.53	30.5[a]
Sharafkhaneh et al	BUD/FF 400/12 vs FF 12	12 months	0.70	1.07	34.6[a]
Kardos et al	FP/Salm 1000/100 vs Salm 100	44 weeks	0.92	1.4	35[a]



TRILOGY



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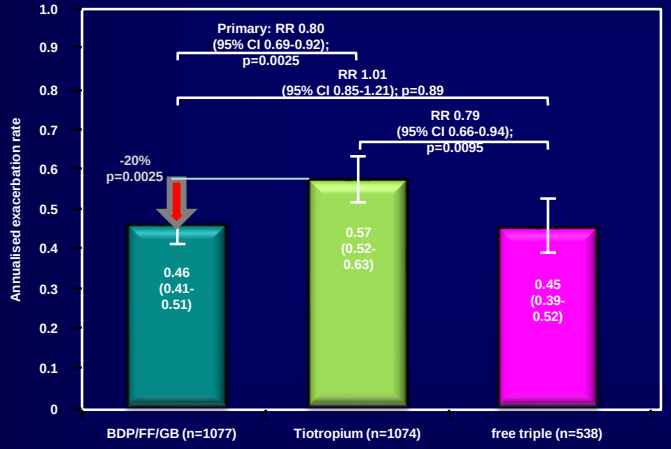

TRIBUTE