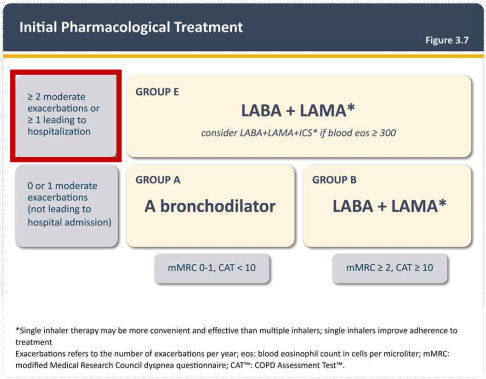
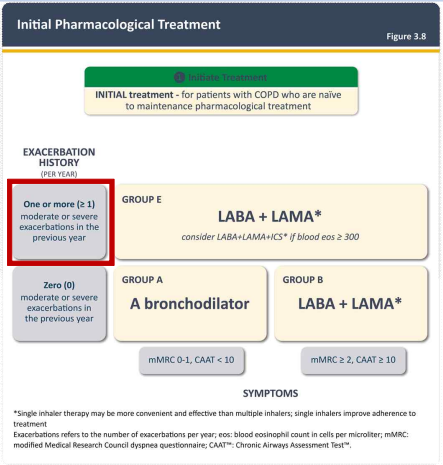
Triple Therapy in ONE Moderate Exacerbation?
“PRO”

가톨릭대학교 호흡기내과
최준영

Recent update in GOLD reports





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3. Should all “one moderate” with high eosinophil use triple?

“One moderate” matters

“One moderate” matters

ELIPSE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Susceptibility to Exacerbation in Chronic Obstructive Pulmonary Disease

Factors Associated with Increased Exacerbation Frequency in the Multivariate Model.

Factor	Number of Exacerbations						P Value for Overall Model
	≥2 vs. 0		1 vs. 0		≥2 vs. 1		
	odds ratio (95% CI)	*P value*	*odds ratio (95% CI)*	*P value*	*odds ratio (95% CI)*	*P value*	
Exacerbation during previous yr — any vs. none	5.72 (4.47–7.31)	<0.001	2.24 (1.77–2.84)	<0.001	2.55 (1.96–3.31)	<0.001	<0.001
FEV_1 — per 100-ml decrease	1.11 (1.08–1.14)	<0.001	1.06 (1.03–1.08)	<0.001	1.05 (1.02–1.09)	<0.001	<0.001
SGRQ score for COPD — per increase of 4 points	1.07 (1.04–1.10)	<0.001	1.01 (0.99–1.04)	0.38	1.06 (1.03–1.09)	<0.001	<0.001
History of reflux or heartburn — yes vs. no	2.07 (1.58–2.72)	<0.001	1.61 (1.23–2.10)	<0.001	1.29 (0.97–1.70)	<0.005	<0.001
White-cell count — per increase of $1\times10^3/mm^3$	1.08 (1.03–1.14)	0.002	1.02 (0.97–1.08)	0.45	1.06 (1.01–1.12)	<0.001	0.007

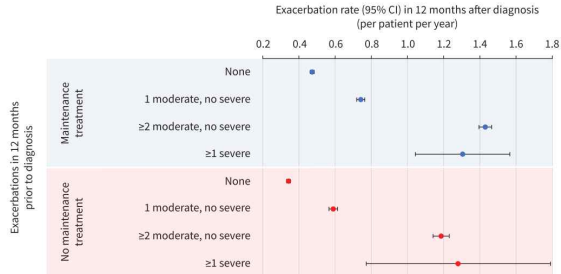
Hurst et al. N Engl J Med. 2010;363(12):1128-38.

“One moderate” matters

EUROPEAN RESPIRATORY JOURNAL
ORIGINAL RESEARCH ARTICLE
D.M.G. HALPIN ET AL.

Exacerbation history and blood eosinophil count prior to diagnosis of COPD and risk of subsequent exacerbations

David M.G. Halpin, Heath Healey, Derek Skinner, Victoria Carter, Rachel Pullen and David Price



Halpin et al. Eur Respir J. 2024;64(4).

Optimum Patient Care Research Database

- Contains medical information on over 24 million patients from over 1000 primary care centres across the UK (~35% of the total UK population

TABLE 3 Rate of moderate and severe exacerbations in the 12 months following diagnosis and incidence rate ratio (IRR) compared to patients with no prior exacerbations, in patients started on maintenance therapy according to history of exacerbations in the 12 months prior to diagnosis and blood eosinophil count (BEC)

Exacerbation history in year prior to diagnosis	Patients (n)	Moderate or severe exacerbations in year following diagnosis	
None			
All	24 267	Rate	0.47 (0.46–0.48)
1 moderate, no severe			
All	9477	Rate	0.74 (0.72–0.76)
		IRR *versus none*	1.57 (1.53–1.61)
BEC <100×10^9 L^{-1}	180	Rate	0.69 (0.53–0.85)
		IRR *versus none*	1.96 (1.65–2.32)
BEC 100–300×10^9 L^{-1}	3615	Rate	0.73 (0.69–0.76)
		IRR *versus none*	1.58 (1.52–1.64)
BEC >300×10^9 L^{-1}	3203	Rate	0.82 (0.78–0.86)
		IRR *versus none*	1.56 (1.49–1.62)
≥2 moderate, no severe			
All	8185	Rate	1.43 (1.39–1.46)
		IRR *versus none*	3.44 (3.35–3.53)
BEC <100×10^9 L^{-1}	144	Rate	1.51 (1.24–1.78)
		IRR *versus none*	4.3 (3.58–5.18)
BEC 100–300×10^9 L^{-1}	3063	Rate	1.37 (1.33–1.42)
		IRR *versus none*	2.96 (2.84–3.25)
BEC >300×10^9 L^{-1}	2842	Rate	1.58 (1.52–1.65)
		IRR *versus none*	3.01 (2.88–3.31)
≥1 severe			
All	161	Rate	1.3 (1.04–1.57)
		IRR *versus none*	2.76 (2.36–3.22)
BEC <100×10^9 L^{-1}	5	Rate	0.6 (0.12–1.08)
		IRR *versus none*	1.71 (0.71–4.12)
BEC 100–300×10^9 L^{-1}	69	Rate	1.16 (0.81–1.51)
		IRR *versus none*	2.52 (1.98–3.19)
BEC >300×10^9 L^{-1}	44	Rate	1.7 (1.1–2.31)
		IRR *versus none*	3.24 (2.41–4.36)

95% are provided confidence intervals for rates and IRRs.

Meta-analysis: Risk after one moderate exacerbation

Open access Original research

BMJ Open

Future exacerbations and mortality rates among patients experiencing COPD exacerbations: a meta-analysis of results from the EXACOS/ AVOIDEX programme

Table 1 Eligibility criteria for the EXACOS/AVOIDEX programme studies, by country

Country	Inclusion criteria
USA	1. Aged ≥40 years. 2. COPD diagnosis is defined as ≥1 code, if inpatient/emergency room and ≥2 codes, if outpatient. 3. Continuous enrolment in Medicare/Medicaid between 2015 and 2018.
Canada	1. Aged ≥65 years (to ensure accurate drug coverage and exacerbation identification). 2. COPD (≥1 code for inpatient or outpatient care).
England	1. Aged ≥40 years. 2. COPD diagnosis. 3. Smoker or ex-smoker. 4. Registered in Clinical Practice Research Datalink.
Scotland	1. Aged ≥40 years. 2. Historic COPD diagnosis based on Read or ICD-10 codes. 3. Had received a respiratory prescription during the baseline period.
Italy	1. Aged ≥40 years. 2. ≥1 COPD diagnosis code (primary or secondary diagnosis; ICD-10 J44) in secondary care.
Spain	1. Aged ≥40 years. 2. ≥1 COPD diagnosis code.
Germany	1. Aged ≥40 years. 2. ≥1 COPD diagnosis code (primary or secondary diagnosis, ICD-10 J44) in primary or secondary care.

Meta-analysis

Rhodes et al.BMJ Open. 2025;15(7):e097006.

Meta-analysis: Mortality and hospitalization risk

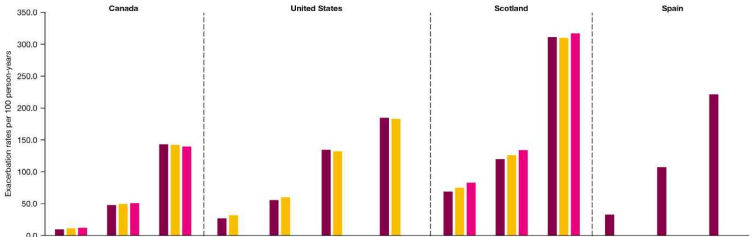
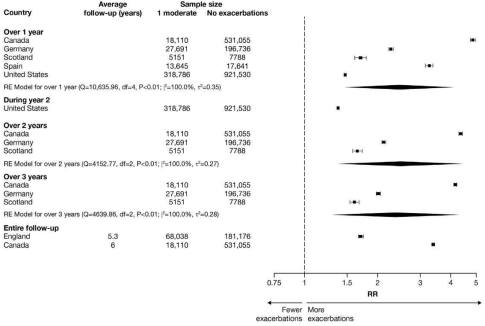
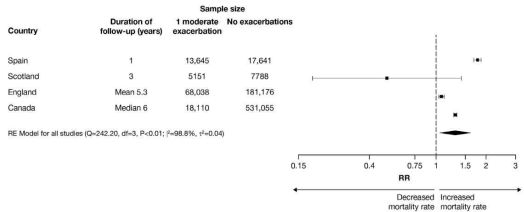


Figure 1 Exacerbation rates per 100 person-years* by baseline exacerbation category. *Includes all studies reporting rates based on over 1, 2 or 3 years of follow-up.

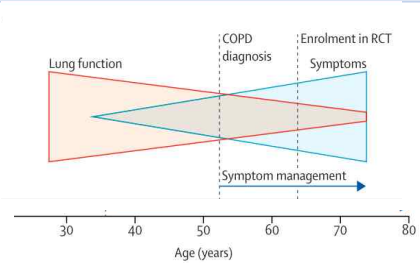
Rhodes et al.BMJ Open. 2025;15(7):e097006.

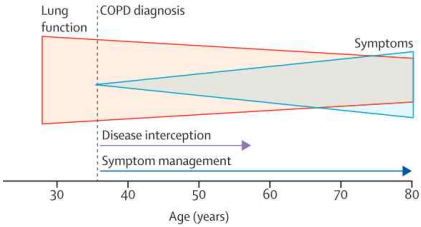




Rhodes et al.BMJ Open. 2025;15(7):e097006.

Early intervention is crucial in patients with COPD





Stolz et al. Lancet. 2022 Sep 17;400(10356):921-972.

New concept in GOLD 2026 : Disease activity in COPD

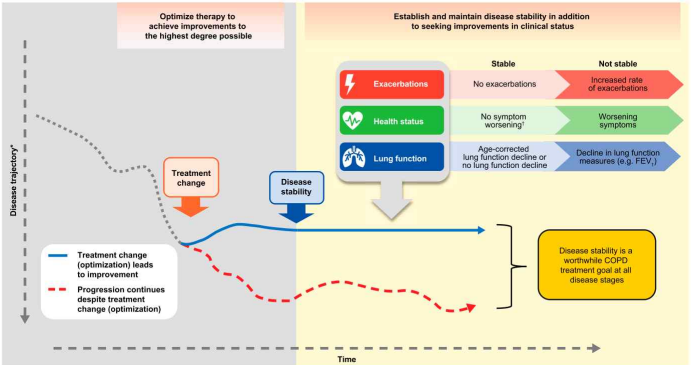
- Treatment Goal : Low disease activity
  - Objective : Prevent exacerbation and organ damage
  - Clinical targets
    - No exacerbations
    - No worsening of symptoms
    - No accelerated loss of lung function
- Key clinical states
  - Disease stability : Low disease activity state
  - Disease control : Low disease activity state + low symptom impact on the patients

Disease stability – new potential treatment goal

CONCISE CLINICAL REVIEW

Is Disease Stability an Attainable Chronic Obstructive Pulmonary Disease Treatment Goal?

Dave Singh[1], MeiLan K. Han[2], Surya P. Bhatt[3], Marc Miravitlles[4], Chris Compton[5], Stefanie Kolterer[6], Tharishini Mohan[6], Suneal K. Sreedharan[6], Lee Tombs[7], and David M. G. Halpin[8]



Singh et al. BLUE 2025;211(3):452-63.

Clinical outcome of disease stability in KOCOSS

[COPD Original Research]

CHEST

Clinical Outcomes in Patients With COPD With Disease Stability

Data from the Korea COPD Subgroup Study Cohort

Eunjeong Son, MD, PhD; Hyewon Seo, MD, PhD; Seung Won Ra, MD, PhD; Seoung Ju Park, MD, PhD; Soo-Jung Um, MD, PhD; Seong Yong Lim, MD, PhD; Hyoung Kyu Yoon, MD, PhD; Kwang Ha Yoo, MD, PhD; Joon Young Choi, MD, PhD; and Chin Kook Rhee, MD, PhD

TABLE 2] Comparison of Exacerbation Frequency According to the Presence of Disease Stability

Exacerbations	IRR	95% CI	*P* Value
Moderate-to-severe	0.30	0.20-0.43	.033
Severe	0.26	0.10-0.58	.002

TABLE 3] Cox Proportional Hazards Regression of All-Cause Mortality According to Disease Stability

	Crude			Multivariate		
Variables	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Disease stability	0.56	0.37-1.09	.096	0.56	0.32-0.96	.036
Age	1.07	1.07-1.11	< .001	1.07	1.05-1.09	< .001
Female sex	0.71	0.34-0.90	.018	0.73	0.32-1.66	.457
BMI	0.87	0.87-0.93	< .001	0.87	0.83-0.91	< .001
Smoking status						
Never		(Reference)			(Reference)	
Prior	1.74	1.12-2.70	.014	1.51	0.73-3.10	.267
Current	1.98	1.25-3.15	.004	2.16	1.02-4.57	.045
HTN	1.27	1.02-1.58	.036	1.49	1.12-2.00	.007
HF	1.78	1.08-2.94	.025	0.70	0.26-1.90	.481
DM	1.00	0.75-1.33	.986			
MI	1.31	0.81-2.10	.269			
CVA	1.27	0.56-2.87	.572			

Son et al. Chest. 2025.

Korean data

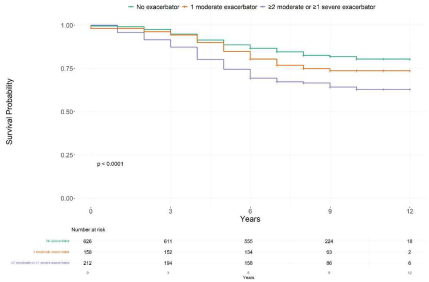
1 moderate exacerbator in KOCOSS

	No exacerbator (N=918)	1 moderate exacerbator (N=241)	2 moderate or 1 severe exacerbator (N=392)	P-value
Age	68.6±7.6	68.8±7.9	69.0±7.2	0.609
Male sex	858 (93.5%)	222 (92.1%)	362 (92.3%)	0.655
BMI	23.2±3.3	23.0±3.4	22.3±3.4	<0.001
Smoking status				0.163
- Never smoker	82 (9.0%)	20 (8.3%)	28 (7.1%)	
- Ex-smoker	598 (65.3%)	145 (60.2%)	271 (69.1%)	
- Current smoker	236 (25.8%)	76 (31.5%)	93 (23.7%)	
mMRC	1.1±0.8	1.4±0.9	1.7±0.9	<0.001
CAT score	12.9±7.4	15.7±7.9	17.7±8.1	<0.001
SGRQ score	27.7±18.8	35.4±21.5	42.9±22.1	<0.001
Past asthma history	244 (26.7%)	59 (24.8%)	147 (37.7%)	<0.001
BEC	218.6±263.4	210.9±184.4	267.0±291.6	0.010
FeNO	26.7±17.3	28.7±13.5	24.5±12.5	0.723
GOLD stage				<0.001
- I	134 (14.7%)	27 (11.2%)	16 (4.1%)	
- II	561 (61.5%)	122 (50.6%)	152 (38.9%)	
- III	189 (20.7%)	80 (33.2%)	183 (46.8%)	
- IV	28 (3.1%)	12 (5.0%)	40 (10.2%)	
Lung function				
- postBD FEV1 (L)	1.8±0.6	1.6±0.6	1.4±0.5	<0.001
- postBD FEV1 (%pred)	61.8±7.2	56.1±18.3	48.5±16.2	<0.001
- postBD FVC (L)	3.4±0.8	3.3±0.7	3.0±0.8	<0.001
- postBD FVC (%pred)	83.2±16.4	80.2±14.9	74.3±16.6	<0.001
- postBD FEV1/FVC (%)	51.7±11.7	48.1±11.9	45.8±11.7	<0.001
DLCo (%pred)	65.9±20.0	63.7±21.8	59.4±20.7	<0.001
RV/TLC	41.7±11.7	43.6±12.9	49.2±12.5	<0.001
6MWD	398.1±115.4	367.3±107.7	347.6±121.5	<0.001
Emphysema on CT	251 (53.0%)	71 (56.8%)	140 (63.6%)	0.030
Bronchiectatsis on CT	91 (19.2%)	25 (20.0%)	35 (15.9%)	0.517
ICS use	271 (34.3%)	90 (43.7%)	207 (56.7%)	<0.001

Moderate-to-severe exacerbation			
Exacerbation group	aIRR	95%CI	p-value
No exacerbation		(Reference)	
1 moderate exacerbation	2.42	1.85-3.17	<0.01
≥2 moderate or ≥1 severe exacerbations	6.55	5.32-8.10	<0.01
Severe exacerbation			
Exacerbation group	aIRR	95%CI	p-value
No exacerbation		(Reference)	
1 moderate exacerbation	2.21	1.27-3.85	<0.01
≥2 moderate or ≥1 severe exacerbations	6.23	4.11-9.58	<0.01

unpublished

1 moderate exacerbator in KOCOSS



Exacerbation group	aHR	95%CI	p-value
All-cause mortality			
No exacerbation		(Reference)	
1 moderate exacerbation	1.49	1.02-2.15	0.04
≥2 moderate or ≥1 severe exacerbations	1.89	1.40-2.55	<0.01
Respiratory-cause mortality			
No exacerbation	(Reference)		
1 moderate exacerbation	3.21	1.76-5.88	<0.01
≥2 moderate or ≥1 severe exacerbations	4.56	2.71-7.65	<0.01

unpublished

Triple therapy in “one moderate” group

Evidences of “1 moderate exacerbation”

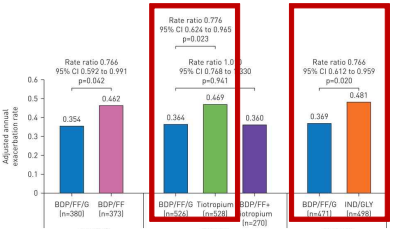
AGORA RESEARCH LETTER

CrossMark

Extrafine triple therapy in patients with symptomatic COPD and history of one moderate exacerbation

Symptomatic COPD
+ severe or very severe airflow limitation,
+ history of one moderate exacerbation

a)



Exacerbation rate

b)

	TRILOGY	TRINITY		TRIBUTE
	BDP/FF/G (n=380) *versus* BDP/FF (n=373)	BDP/FF/G (n=526) *versus* Tiotropium (n=528)	BDP/FF/G (n=526) *versus* BDP/FF + tiotropium (n=270)	BDP/FF/G (n=471) *versus* IND/GLY (n=498)
Week 52 SGRQ total score				
Mean	−3.97 (−5.92 to −2.02) p<0.001	−1.43 (−3.12 to 0.26) p=0.098	1.64 (−0.39 to 3.68) p=0.114	−2.14 (−3.63 to −0.65) p=0.005
Responders	1.54 (1.14 to 2.09) p=0.006	1.22 (0.94 to 1.58) p=0.133	0.92 (0.67 to 1.26) p=0.604	1.38 (1.05 to 1.80) p=0.020
Overall mean SGRQ total score	−2.91 (−4.29 to −1.52) p<0.001	−1.86 (−3.10 to −0.62) p=0.003	0.51 (−1.00 to 2.01) p=0.509	−2.16 (−3.23 to 1.08) p<0.001
Week 52 pre-dose morning FEV₁ mL	83 (42 to 123) p<0.001	52 (16 to 88) p=0.005	−16 (−59 to 27) p=0.470	25 (−5 to 55) p=0.103
Overall pre-dose morning FEV₁ mL	93 (62 to 124) p<0.001	41 (13 to 68) p=0.003	−26 (−58 to 7) p=0.128	28 (6 to 51) p=0.014

Singh et al. ERJ. 2019;53(5).

IMPACT trial: Triple vs. dual therapy in moderate exacerbators

ORIGINAL ARTICLE
COPD

The effect of exacerbation history on outcomes in the IMPACT trial

IMPACT trial

- A 52-week, randomised, double-blind trial,
- FF/UMEC/VI versus FF/VI or UMEC/VI in patients with symptomatic COPD and a history of exacerbations.

	Subgroup		
	Single moderate	**Frequent moderate**	**Severe**
Subjects	3056 [30]	4628 [45]	2671 [26]
Age years	65.2±7.95	65.3±8.46	65.4±8.29
Male	2069 [68]	2922 [63]	1879 [70]
White	2408 [79]	3604 [78]	1971 [74]
Former smoker	1964 [64]	3014 [65]	1790 [67]
BMI kg·m^{-2}	26.10±6.043	27.03±5.833	26.52±6.532
Lung function post-bronchodilator			
At screening FEV_1 L	1.046±0.3193	1.437±0.5036	1.247±0.5037
FEV_1 % predicted	37.0±8.85	51.9±14.77	44.4±15.25
FEV_1/FVC ratio	0.421±0.1028	0.510±0.1161	0.458±0.1201
Baseline® concomitant COPD medication at screening alone or in combination			
LAMA	243 [8]	375 [8]	213 [8]
LABA	84 [3]	166 [4]	41 [2]
LAMA+LABA	327 [11]	392 [8]	215 [8]
ICS+LABA	906 [30]	1694 [37]	741 [28]
ICS+LAMA+LABA	1258 [41]	1651 [36]	1274 [48]
Baseline blood eosinophil counts	203±186	230±256	232±242
Patients with count %			
<100	26	25	24
100–300	55	53	52
>300	19	23	23

Halpin et al. Eur Respir J. 2020;55(5).

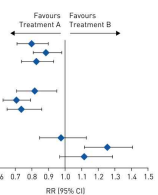
IMPACT trial: Exacerbation reduction with triple therapy

IMPACT trial

Moderate-to-severe exacerbations

a)

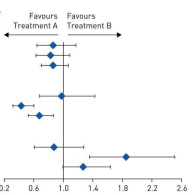
	Treatment A FF/UMEC/VI	Treatment B FF/VI	RR (95% CI)	p-value
FF/UMEC/VI *versus* FF/VI				
Single moderate subgroup	0.85 [0.78–0.92]	1.06 [0.97–1.15]	0.80 [0.71–0.90]	<0.001
Frequent moderate subgroup	0.85 [0.80–0.91]	0.96 [0.90–1.03]	0.89 [0.81–0.98]	0.016
Severe subgroup	1.06 [0.98–1.16]	1.28 [1.18–1.39]	0.83 [0.74–0.93]	0.002
FF/UMEC/VI *versus* UMEC/VI	**FF/UMEC/VI**	**UMEC/VI**		
Single moderate subgroup	0.85 [0.78–0.92]	1.03 [0.92–1.14]	0.82 [0.71–0.95]	0.007
Frequent moderate subgroup	0.85 [0.80–0.91]	1.21 [1.10–1.32]	0.71 [0.63–0.79]	<0.001
Severe subgroup	1.06 [0.98–1.16]	1.43 [1.27–1.61]	0.74 [0.65–0.86]	<0.001
UMEC/VI *versus* FF/VI	**UMEC/VI**	**FF/VI**		
Single moderate subgroup	1.03 [0.92–1.16]	1.06 [0.97–1.15]	0.98 [0.85–1.13]	0.782
Frequent moderate subgroup	1.21 [1.10–1.32]	0.96 [0.90–1.03]	1.26 [1.12–1.41]	<0.001
Severe subgroup	1.43 [1.27–1.61]	1.28 [1.18–1.39]	1.12 [0.97–1.29]	0.129



Severe exacerbations

b)

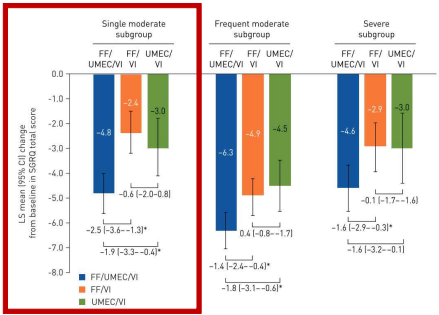
	Treatment A FF/UMEC/VI	Treatment B FF/VI	RR (95% CI)	p-value
FF/UMEC/VI *versus* FF/VI				
Single moderate subgroup	0.11 [0.09–0.14]	0.13 [0.10–0.16]	0.88 [0.66–1.18]	0.388
Frequent moderate subgroup	0.06 [0.05–0.08]	0.07 [0.06–0.09]	0.84 [0.64–1.10]	0.198
Severe subgroup	0.29 [0.25–0.33]	0.33 [0.28–0.38]	0.88 [0.72–1.08]	0.226
FF/UMEC/VI *versus* UMEC/VI	**FF/UMEC/VI**	**UMEC/VI**		
Single moderate subgroup	0.11 [0.09–0.14]	0.11 [0.08–0.15]	0.99 [0.69–1.43]	0.962
Frequent moderate subgroup	0.06 [0.05–0.08]	0.14 [0.11–0.17]	0.45 [0.33–0.61]	<0.001
Severe subgroup	0.29 [0.25–0.33]	0.42 [0.34–0.51]	0.69 [0.54–0.88]	0.003
UMEC/VI *versus* FF/VI	**UMEC/VI**	**FF/VI**		
Single moderate subgroup	0.11 [0.08–0.15]	0.13 [0.10–0.16]	0.89 [0.62–1.28]	0.519
Frequent moderate subgroup	0.14 [0.11–0.17]	0.07 [0.06–0.09]	1.86 [1.37–2.51]	<0.001
Severe subgroup	0.42 [0.34–0.51]	0.33 [0.28–0.38]	1.28 [1.00–1.64]	0.048



Halpin et al. Eur Respir J. 2020;55(5).

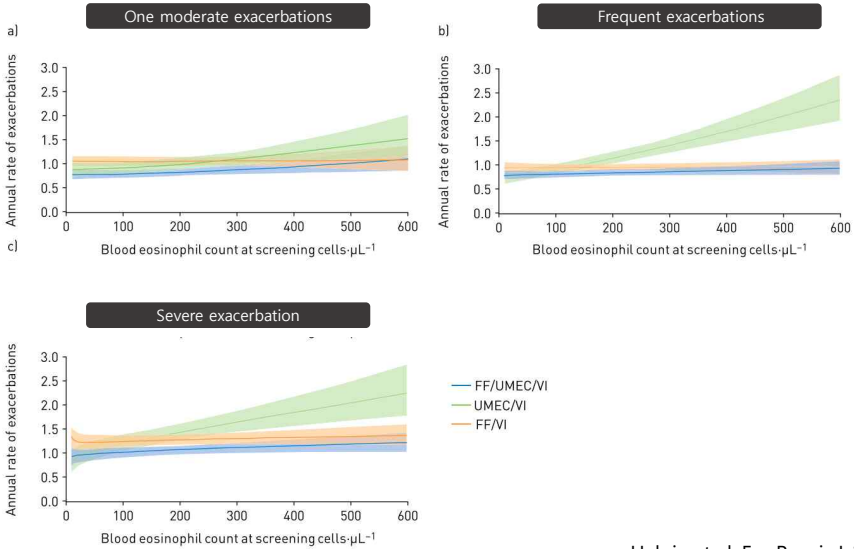
IMPACT trial: Quality of life outcomes (SGRQ)

IMPACT trial



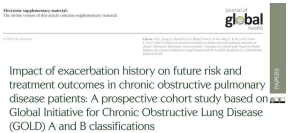
SGRQ change

Halpin et al. Eur Respir J. 2020;55(5).



Halpin et al. Eur Respir J. 2020;55(5).

RealDTC: Exacerbation patterns in Chinese COPD cohort


Electronic supplementary material:
The online version of this article contains supplementary material.

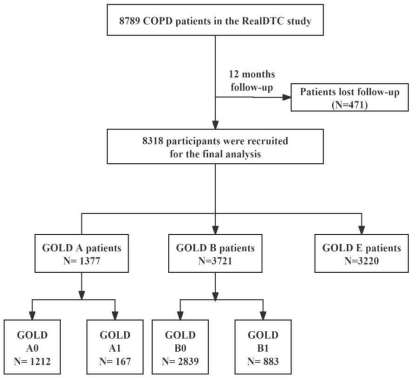
journal of global health

Impact of exacerbation history on future risk and treatment outcomes in chronic obstructive pulmonary disease patients: A prospective cohort study based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) A and B classifications

PAPERS

- This observational study was based on the cohort study RealDTC.
- Data from COPD patients in China from 2017-2022.
- GOLD A0 and B0, who had no exacerbation during the previous year,
- GOLD A1 and B1, who had only one exacerbation during the previous year.

RealDTC



Lin et al. J Glob Health. 2024;14:04202.

RealDTC: Exacerbation patterns in Chinese COPD cohort

Table 4. Hazard ratios for exacerbation and mortality for GOLD A1 vs A0*

	Moderate-to-severe exacerbation		Hospitalisation		Frequent exacerbation		Mortality	
Group	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
A0	Ref.		Ref.		Ref.		Ref.	
A1	2.087 (1.419–3.068)	<0.001	1.704 (1.010–2.705)	0.045	1.983 (1.046–3.709)	0.036	2.213 (0.775–9.087)	0.134

CI – confidence interval, GOLD – Global Initiative for Chronic Obstructive Lung Disease, HR – hazard ratio, ref – reference
*Age, gender, education, BMI, smoking status, comorbidities, FEV1% predicted, CAT, and PDC were included as the variables in the multivariate Cox analysis.

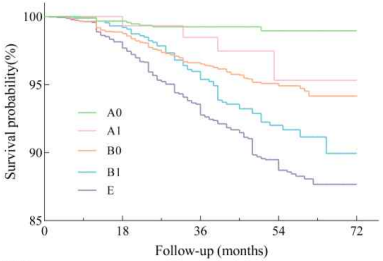
Table 5. Hazard ratios for exacerbation and mortality for GOLD B1 vs B0*

	Moderate-to-severe exacerbation		Hospitalisation		Frequent exacerbation		Mortality	
Group	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
B0	Ref.		Ref.		Ref.		Ref.	
B1	1.321 (1.105–1.679)	0.003	0.985 (0.773–1.286)	0.652	0.973 (0.799–1.421)	0.473	1.362 (1.026–1.963)	0.041

CI – confidence interval, GOLD – Global Initiative for Chronic Obstructive Lung Disease, HR – hazard ratio, ref – reference
*Age, gender, education, BMI, smoking status, comorbidities, FEV1% predicted, CAT, and PDC were included as the variables in the multivariate Cox analysis.

Lin et al. J Glob Health. 2024;14:04202.

RealDTC: Risk factors for exacerbation progression



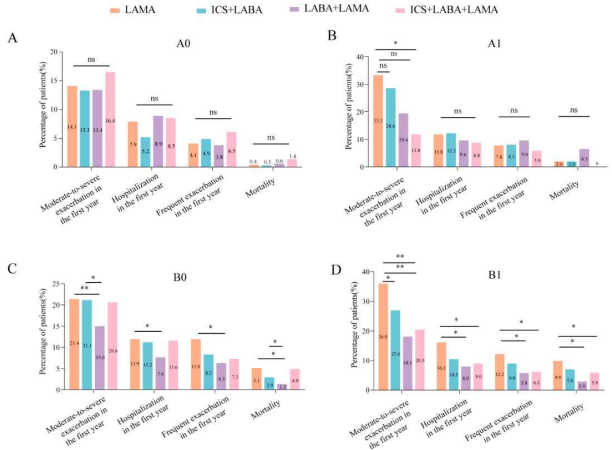
Number at risk

A0	1212	1009	615	188	4
A1	165	147	105	27	1
B0	2839	2622	1959	798	27
B1	882	844	645	273	11
E	3220	2935	2078	738	18

Figure 3. The Kaplan-Meier graphs for mortality in GOLD A1, A1, B0, B1, E.

Lin et al. J Glob Health. 2024;14:04202.

RealDTC: Outcomes by exacerbation history



Lin et al. J Glob Health. 2024;14:04202.

RealDTC: Clinical implications for "one moderate" patients

Table 6. Hazard ratios of different inhalation drugs for future exacerbation and mortality in groups A0, A1, B0, and B1

	Moderate-to-severe exacerbation		Hospitalisation		Frequent exacerbation		Mortality	
Group and inhalation drug	HR (95% CI)	*P*-value	HR (95CI%)	*P*-value	HR (95CI%)	*P*-value	HR (95CI%)	*P*-value
A0								
LABA	Ref.		Ref.		Ref.		Ref.	
ICS+LABA	0.924 (0.627–1.386)	0.762	1.114 (0.596–1.642)	0.711	1.053 (0.784–1.423)	0.763	1.098 (0.011–6.486)	0.968
LABA+LAMA	0.933 (0.588–1.592)	0.782	0.976 (0.821–1.469)	0.563	1.122 (0.684–1.742)	0.838	2.621 (0.238–9.362)	0.662
ICS+LABA+LAMA	1.048 (0.689–1.536)	0.578	0.990 (0.678–1.398)	0.875	1.013 (0.667–1.875)	0.646	3.465 (0.757–10.869)	0.187
A1								
LABA	Ref.		Ref.		Ref.		Ref.	
ICS+LABA	0.818 (0.335–1.996)	0.659	0.909 (0.477–2.641)	0.361	1.191 (0.150–4.439)	0.869	1.021 (0.110–6.982)	0.970
LABA+LAMA	1.043 (0.371–2.935)	0.936	0.928 (0.238–3.337)	0.806	0.912 (0.420–2.523)	0.230	1.063 (0.203–8.336)	0.672
ICS+LABA+LAMA	0.277 (0.083–0.930)	0.038	0.945 (0.237–3.751)	0.848	1.117 (0.240–3.320)	0.540	0.927 (0.511–2.479)	0.378
B0								
LABA	Ref.		Ref.		Ref.		Ref.	
ICS+LABA	1.004 (0.760–1.328)	0.976	0.942 (0.658–1.348)	0.743	0.853 (0.530–1.373)	0.513	0.417 (0.203–0.856)	0.017
LABA+LAMA	0.69 (0.453–0.932)	0.019	0.607 (0.376–0.979)	0.041	0.416 (0.218–0.796)	0.008	0.209 (0.062–0.713)	0.012
ICS+LABA+LAMA	0.935 (0.751–1.165)	0.551	0.950 (0.719–1.254)	0.711	0.659 (0.447–0.970)	0.035	0.787 (0.508–1.218)	0.283
B1								
LABA	Ref.		Ref.		Ref.		Ref.	
ICS+LABA	0.770 (0.445–1.334)	0.351	0.459 (0.205–1.028)	0.058	0.713 (0.312-1.629)	0.422	0.415 (0.140–1.233)	0.113
LABA+LAMA	0.400 (0.212–0.753)	0.005	0.532 (0.235–0.987)	0.040	0.395 (0.145–1.072)	0.068	0.339 (0.089–1.279)	0.110
ICS+LABA+LAMA	0.448 (0.266–0.755)	0.003	0.463 (0.230–0.933)	0.031	0.337 (0.146–0.776)	0.011	0.257 (0.083–0.796)	0.019

Lin et al. J Glob Health. 2024;14:04202.

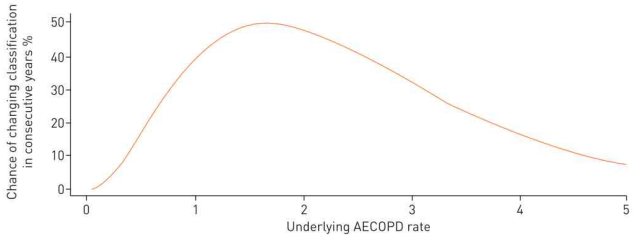
Should all “one moderate” with high eosinophil use triple?

Annual event counts can be noisy

ORIGINAL ARTICLE
COPD

Should the number of acute exacerbations in the previous year be used to guide treatments in COPD?

- Exacerbation events occur randomly even with a stable underlying risk.
- Example: a patient with ~1.5 exacerbations/year may have 0–3 events in different years by chance.
- Therefore, the frequent exacerbator classification can change 30–45% between consecutive years.



WISDOM trial: ICS withdrawal in stable COPD

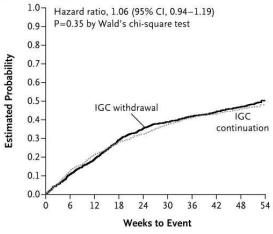
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 2, 2014 VOL. 371 NO. 14

Withdrawal of Inhaled Glucocorticoids and Exacerbations of COPD

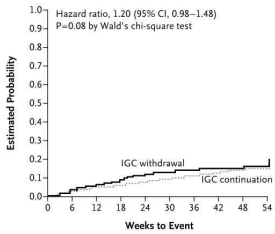
Helgo Magnussen, M.D., Bernd Disse, M.D., Ph.D., Roberto Rodriguez-Roisin, M.D., Anne Kirsten, M.D., Henrik Watz, M.D., Kay Tetzlaff, M.D., Lesley Towse, B.Sc., Helen Finnigan, M.Sc., Ronald Dahl, M.D., Marc Decramer, M.D., Ph.D., Pascal Chanez, M.D., Ph.D., Emiel F.M. Wouters, M.D., Ph.D., and Peter M.A. Calverley, M.D., for the WISDOM Investigators*

A Moderate or Severe COPD Exacerbation



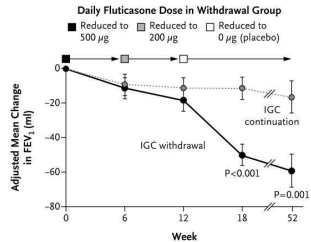
No. at Risk										
IGC continuation	1243	1059	927	827	763	694	646	615	581	14
IGC withdrawal	1242	1090	965	825	740	688	646	607	570	19

C Severe COPD Exacerbation



No. at Risk										
IGC continuation	1243	1180	1117	1066	1026	993	957	928	895	20
IGC withdrawal	1242	1189	1119	1044	986	941	918	889	863	25

D Change from Baseline in Trough FEV_1



No. at Risk					
IGC continuation	1223	1135	1114	1077	970
IGC withdrawal	1218	1135	1092	1058	935

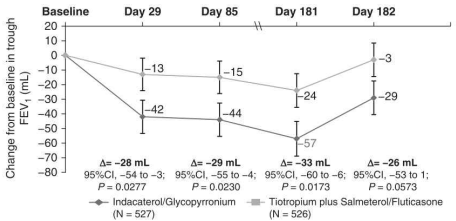
Magnussen et al. N Engl J Med. 2014;371(14):1285-94.

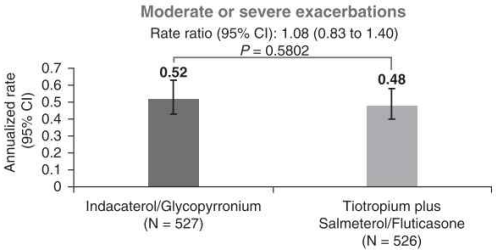
SUNSET study: ICS withdrawal in stable COPD

ORIGINAL ARTICLE

Long-Term Triple Therapy De-escalation to Indacaterol/ Glycopyrronium in Patients with Chronic Obstructive Pulmonary Disease (SUNSET): A Randomized, Double-Blind, Triple-Dummy Clinical Trial

Kenneth R. Chapman[1*], John R. Hurst[2*], Stefan-Marian Frent[3†], Michael Larbig[4], Robert Fogel[5], Tadhg Guerin[6], Donald Banerji[6], Francesco Patalano[6], Pankaj Goyal[6], Pascal Pfister[6], Konstantinos Kostikas[6], and Jadwiga A. Wedzicha[7]





Chapman et al. BLUE 2018;198(3):329-39.

Rethinking GOLD E

ARTICLE IN PRESS

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Review Article

Rethinking GOLD E: The Significance of a Single Moderate Exacerbation in COPD

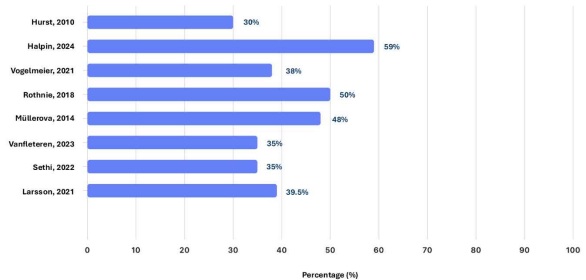
Marc Miravitlles

Pneumology Department, Vall d'Hebron University Hospital/Vall d'Hebron Research Institute (VHIR), Vall d'Hebron-Barcelona Hospital Campus, CIBER de Enfermedades Respiratorias (CIBERES), Barcelona, Spain

Table 1
Characteristics of studies reporting risk of an exacerbation over a year follow-up of patients with one moderate exacerbation in the previous year.

Authors, year (ref.)	*N* and country	Mean age	Mean FEV1 (%)	PROs	CVD
Larsson, 2021 [17]	18,586 Sweden	68.2–69.5	61.4%–65.1%	NR	35.6%–41.6%
Sethi, 2022 [6]	1,492,108 US	70.9	NR	NR	38%
Vanfleteren, 2023 [15]	45,350 Sweden	71.5	60.4%	CAT: 13.2	18.4%
Müllerova, 2014 [18]	58,589 UK	69.5	60%	NR	10%
Rothnie, 2018 [14]	99,574 UK	66.9	62.1%	NR	14.5%
Vogelmeier, 2021 [19]	250,723 Germany	63	NR	NR	38%
Halpin, 2024 [20]	15,717 UK	66.1	NR	CAT: >10 61%	5.8%
Hurst, 2010 [1]	International 2,138	63	48%	SGRQ: 50	NR

US: United States; UK: United Kingdom; FEV1: forced expiratory volume in one second; PROs: patient reported outcomes; CVD: cardiovascular disease: NR: not reported; CAT: COPD Assessment Test; SGRQ: St. George's Respiratory Questionnaire.



Miravitlles et al. Arch Bronconeumol. 2026.

Different group in “new” GOLD E

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Review Article

Rethinking GOLD E: The Significance of a Single Moderate Exacerbation in COPD

Marc Miravitlles

COPD Patients

Patient A

Age 57

FEV_1 72%

No comorbidities

1 moderate exacerbation

GOLD E1.

Patient B

Age 77

FEV_1 41%

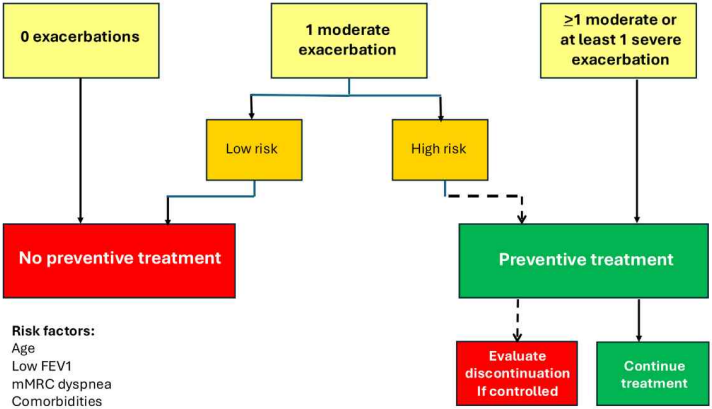
CV comorbidity

1 moderate exacerbation

GOLD E2.

Miravitlles et al. Arch Bronconeumol. 2026.

Practical approach to triple therapy initiation



Miravitlles et al. Arch Bronconeumol. 2026.

Take Home Messages

1. **A single moderate exacerbation is not benign.**
   Even one moderate exacerbation predicts a higher risk of future exacerbations, hospitalization, and mortality.
2. **Recent GOLD updates emphasize earlier risk recognition.**
   The definition of high-risk exacerbators now highlights that even one moderate event may warrant closer therapeutic consideration.
3. **Clinical trials support triple therapy benefits in one moderate exacerbator group.**
   Studies such as IMPACT show reductions in moderate-to-severe exacerbations and improvements in quality of life.
4. **Real-world cohort data confirm progression risk after a single exacerbation.**
   Observational studies demonstrate that patients with one moderate event frequently progress to recurrent exacerbations.
5. **Patient selection remains critical.**
   Blood eosinophil levels help identify patients most likely to benefit from ICS-containing triple therapy. Risk factors should be considered before starting preventive treatment.