Triple Therapy in One Moderate Exacerbation?

Con: Rethinking Uniform Escalation to Triple Therapy After a Single Moderate Exacerbation

Sun Hye Shin

Assistant professor

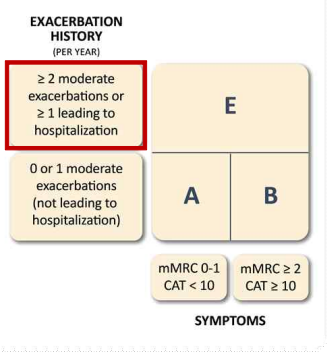
Division of pulmonary and critical care medicine

Department of internal medicine

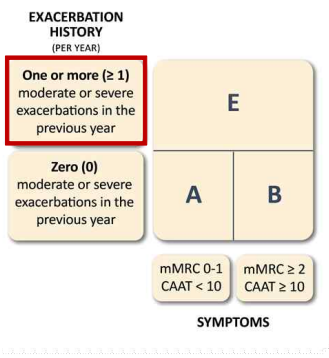
Samsung Medical Center, Sungkyunkwan University School of Medicine

Initial assessment: ABE tool

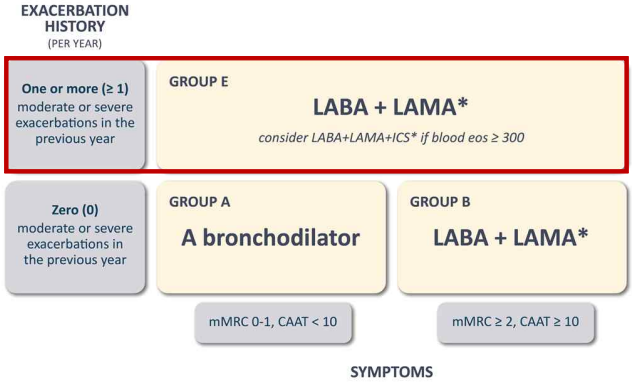
2017 – 2025



2026

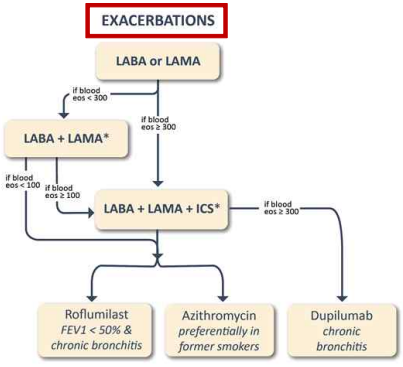


Initial pharmacologic treatment in GOLD 2026



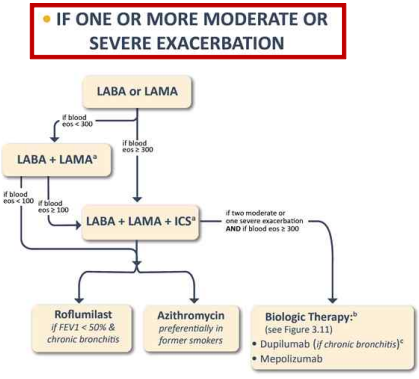
Follow-up treatment algorithm in 2026

2019 – 2025



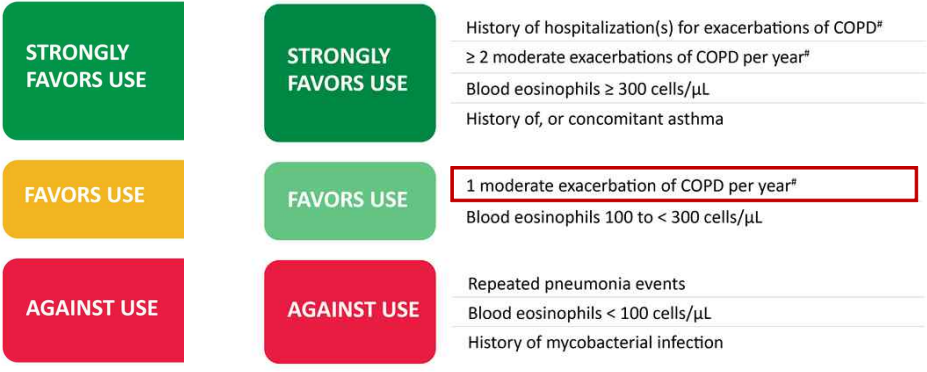
*In patients who develop **further exacerbations** on LAMA+LABA therapy, we suggest escalation to LABA+LAMA+ICS.*

2026

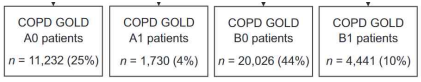


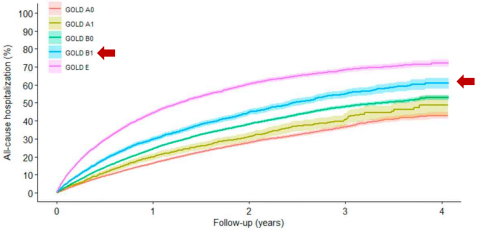
*In patients who have **a moderate or severe exacerbation** on LAMA+LABA therapy, we suggest escalation to LABA+LAMA+ICS.*

Factors to consider when initiating ICS



One moderate AE → Increased future risk





Swedish National Airway Register

UK primary care database (OPCRD)

Vanfleteren et al. AJRCCM. 2023;208(2):163-175
Halpin et al. Eur Respir J 2024; 64(4):2302240.

I

High risk in one moderate AE = Benefit of Triple therapy ?

No evidence for the benefit of Triple therapy after 1 Mod AE

ORIGINAL ARTICLE

DOI: 10.1016/j.arbres.2024.04.008 Full text access

Triple Therapy and Clinical Control in B+ COPD Patients: A Pragmatic, Prospective, Randomized Trial

B+ patient definition (n=1028)

- Female or male
- 40-80 yrs. of age
- Current/former smokers ≥10 pack-year
- COPD (GOLD 2024) with FEV1 post-BD 30-70% of the reference value
- B+ phenotype:
  - ✓ CAT≥10 despite being on LABA/LAMA for ≥3 months, *and*
  - ✓ 1 moderate ECOPD in the previous year (treated with a short course of oral steroids and/or antibiotics), *and*
  - ✓ ≥150 blood Eos/mL (as determined by a single Eos measurement in the previous 12 months available in the medical record of the patient)
- No ICS or exacerbation >8 weeks before randomization

Terminated

Delays in the opening and activation of participating sites, and a low recruitment rate, with only 48 participants enrolled over the course of one year

ANTES B+ Clinical Trial (ANTES B+)

ClinicalTrials.gov ID NCT06282861

Sponsor Fundacio Privada Mon Clinic Barcelona

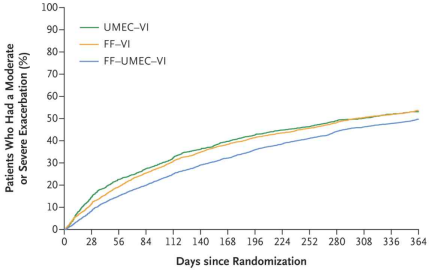
Information provided by Fundacio Privada Mon Clinic Barcelona (Responsible Party)

Last Update Posted 2025-08-14

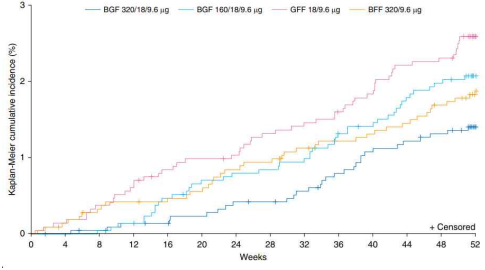
Agusti et al. Archivos de bronconeumologia. 2024;60:417-22.

Benefit of triple therapy in “High-risk” patients

IMPACT



ETHOS



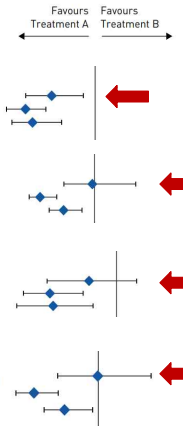
- Reduction in exacerbation & mortality with triple therapy
- Conducted in high-risk patients with frequent exacerbation

Lipson et al. N Engl J Med. 2018;378(18):1671-1680.
Rabe et al. N Engl J Med. 2020;383(1):35-48.

IMPACT: post-hoc analysis in subgroup with 1 mod AE

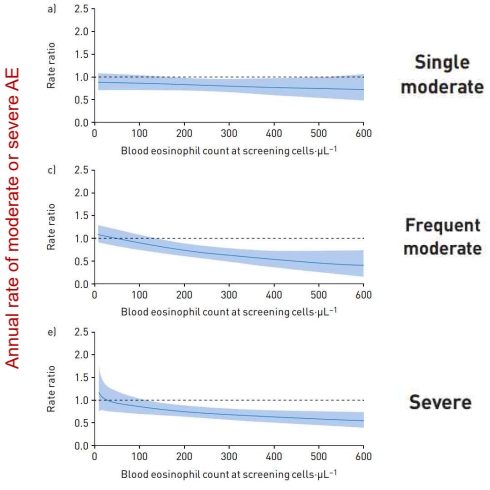
30% of study population

	Treatment A FF/UMEC/VI	Treatment B FF/VI	RR (95% CI)	p-value
Annual rate of moderate or severe AE				
FF/UMEC/VI *versus* UMEC/VI	**FF/UMEC/VI**	**UMEC/VI**		
Single moderate subgroup	0.85 (0.78–0.92)	1.03 (0.92–1.16)	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
Annual rate of severe AE				
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
Time-to-first moderate or severe AE				
FF/UMEC/VI *versus* UMEC/VI	**FF/UMEC/VI**	**UMEC/VI**		
Single moderate subgroup	545/1198 (45)	281/616 (46)	0.92 (0.79–1.06)	0.246
Frequent moderate subgroup	859/1866 (46)	478/939 (51)	0.80 (0.72–0.90)	<0.001
Severe subgroup	555/1087 (51)	277/515 (54)	0.81 (0.70–0.93)	0.003
Time-to-first severe AE				
FF/UMEC/VI *versus* UMEC/VI	**FF/UMEC/VI**	**UMEC/VI**		
Single moderate subgroup	112/1198 (9)	55/616 (9)	1.00 (0.72–1.38)	0.978
Frequent moderate subgroup	117/1866 (6)	96/939 (10)	0.55 (0.42–0.72)	<0.001
Severe subgroup	218/1087 (20)	121/515 (23)	0.77 (0.62–0.96)	0.021



Halpin et al. Eur Respir J. 2020;55(5):1901921

IMPACT: post-hoc analysis in subgroup with 1 mod AE

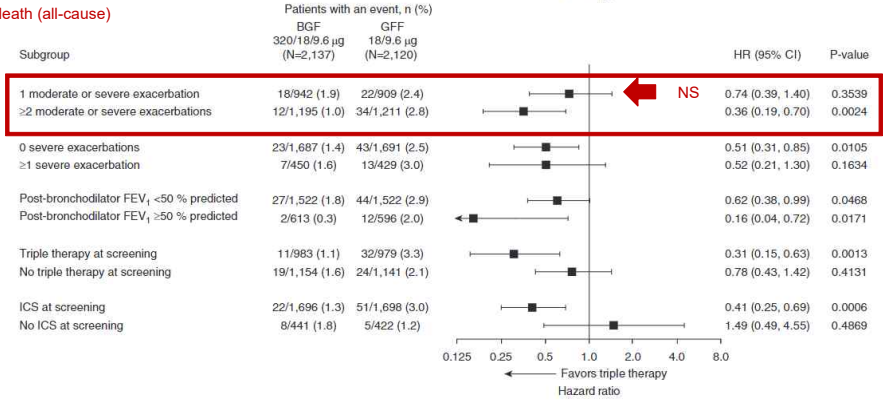


Halpin et al. Eur Respir J. 2020;55(5):1901921

ETHOS: post-hoc analysis in subgroup with 1 mod AE

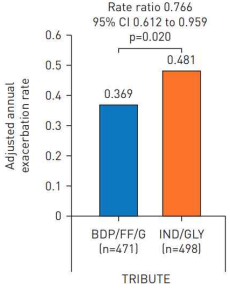
40% of study population

Time to death (all-cause)

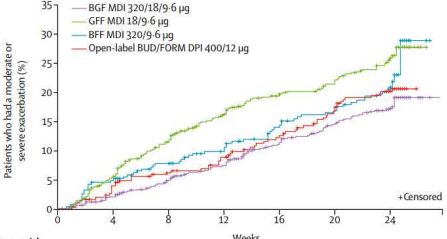


Benefit of Triple over Dual in 1 mod AE group

TRIBUTE Subgroup with 1 mod AE



KRONOS 74% had no AE, 19% had 1 AE



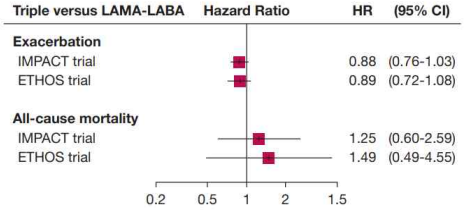
Number at risk							
BGF MDI 320/18/9·6 µg	639	620	590	561	526	498	428
GFF MDI 18/9·6 µg	625	585	532	492	463	446	371
BFF MDI 320/9·6 µg	314	295	277	260	242	233	196
Open-label BUD/FORM DPI 400/12 µg	318	297	282	271	257	241	203

Singh et al. Eur Res J 2019 53: 1900235
Ferguson et al. Lancet Respir Med. 2018;6(10):747-758.

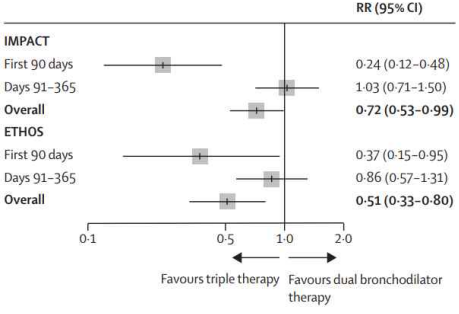
ICS withdrawal issue

Discontinue ICSs in the IMPACT (70%), ETHOS (80%), and TRIBUTE (65%) trials.

ICS naïve patients

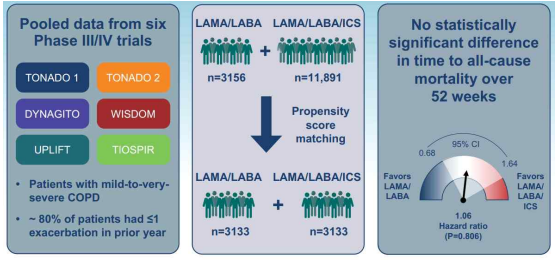


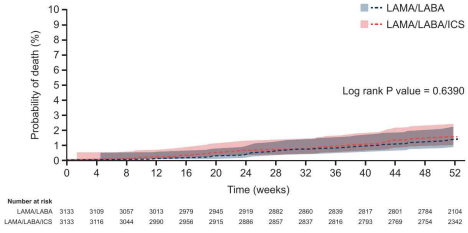
Mortality over time



Suissa et al. Lancet Respir Med 2021; 9: 684-685.
Suissa et al. Chest 2024; 166: 17-20.

Pooled analysis in ICS-naïve patients





36% had no AE

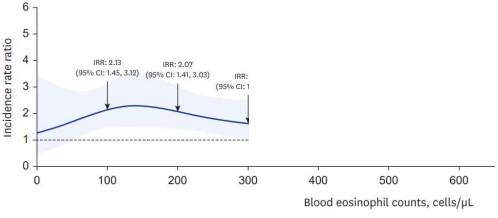
45% had one mod AE

Int J Chron Obstruct Pulmon Dis 2022; 17: 545-558.

Korean COPD Subtype Study (KOCOSS) data

Group B patients

Eos < 300 (n = 328) : **16.5%** had 1 moderate AE



→ TT was associated with higher risk of AE in Eos < 300

→ TT was not associated with lower risk of AE even in Eos >300

Group A patients (n = 286)

8.4% had 1 moderate AE

	No (%) of Patients with Moderate or Severe Exacerbation during 1-Year Follow-Up Period	Odds Ratio (95% Confidence Interval)			
		Crude	Model 1	Model 2	Model 3
Without ICS (*N* = 191)	41 (21.5)	Reference	Reference	Reference	Reference
With ICS (*N* = 95)	25 (26.3)	1.31 (0.74–2.32)	1.22 (0.66–2.26)	1.24 (0.67–2.31)	1.37 (0.67–2.78)

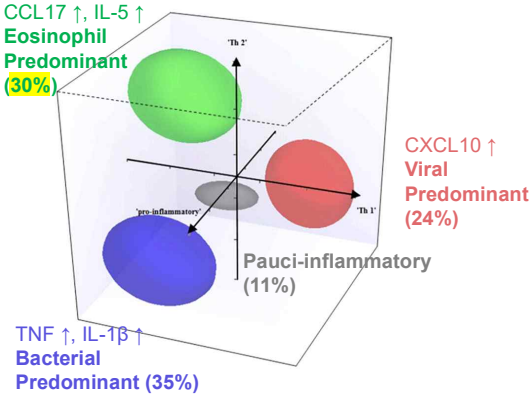
→ ICS was not associated with lower risk (regardless of Eos)

Song et al. J Korean Med Sci 2025; 40: e147.
Shin et al. J Pers Med. 2022;12(6):916.

II

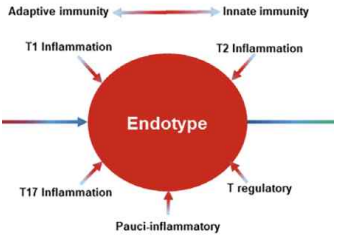
Are All COPD Exacerbations the Same?

Heterogeneous biology of COPD exacerbations



Bafadhel et al. AJRCCM 2011; 184: 662-671.

Biomarkers for Exacerbation Endotype

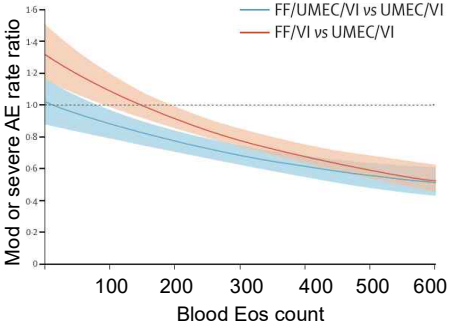


Exacerbation Endotype	Biomarkers	Additional tests
T1 inflammation	Viral PCR (e.g., nasopharyngeal swab single tests or panels)	CXCL10 (serum/sputum) CXCL11 (sputum) IFN-γ (sputum) Sputum microbiome: greater proportions of Actinobacteria and Firmicutes at the phylum level, decreased proportion of proteobacteria*
		Volatile organic compounds using eNose*
		Gene expression signatures*
T2 inflammation	Eosinophils (blood/sputum) F_{ENO}	Sputum microbiome: greater Bacteroidetes at phylum level* Sputum microbiome: greater α diversity*
		IL-5 (sputum/serum) CCL17 (sputum) IL-13 (sputum) CCL17 (sputum) CCL26 (serum) Eotaxin-3 (sputum/plasma)
		Gene expression signatures*
T17 inflammation	Neutrophil (sputum/blood) C-reactive protein (serum) Sputum Gram stain and culture Procalcitonin	Sputum microbiome: higher bacterial load* Sputum microbiome: greater Proteobacteria at phylum level* TNFa (sputum) IL-β (sputum) C-reactive protein (serum) IL-6 (serum) TNF-R1, TNF-R2 (serum) IL-8 (sputum) Amyloid A (serum)
		Gene expression signatures*
Pauciinflammatory	—	Look for alternative causes

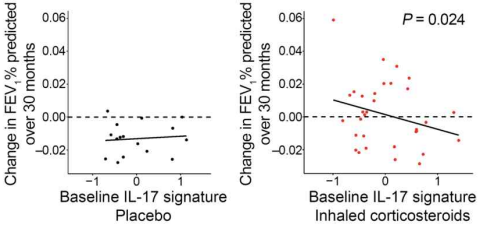
Bhatt et al. AJRCCM 2023; 208: 1026-1041.

Divergent responses to ICS addition

IMPACT



GLUCOLD



IL-17 high was associated with lack of response to ICS at 30 months

Pascoe et al. Lancet Respir Med. 2021;9(12):e114.
Christenson et al. J Clin Invest 2019; 129: 169-181.

Treatment for moderate exacerbation

1. 정의와 분류

COPD의 급성악화는 'COPD 환자의 기본적인 호흡기증상이 매일-매일의 변동범위를 넘어서 치료약제의 추가가 필요할 정도로 급격히 악화된 상태'로 정의하며[172, 636-638], 경증, 중등증, 중증 악화로 분류한다[639].

- 경증 악화: 속효성 기관지확장제 치료만 필요한 경우
- 중등증 악화: 속효성 기관지확장제와 항생제 또는 경구스테로이드 치료가 필요한 경우
- 중증 악화: 응급실 방문이나 입원이 필요한 악화이며 급성 호흡부전을 동반할 수 있다.

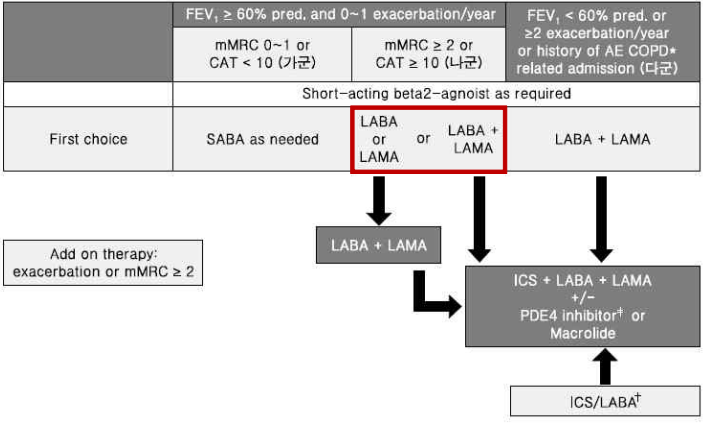
대한결핵 및 호흡기학회 COPD 진료 지침

기침/가래가 주된 악화 (항생제)

호흡곤란이 주된 악화 (스테로이드)

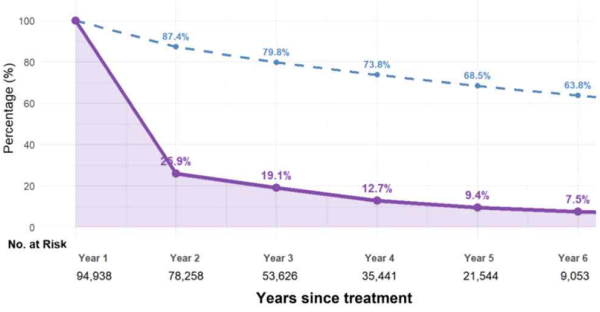
2018 한국 진료 지침

• 안정 시 COPD의 약물 단계치료



Korean NHIS data

- 94,938 patients received **LAMA/LABA as the first treatment** of COPD (2018 – 2022)



High LAMA/LABA maintenance

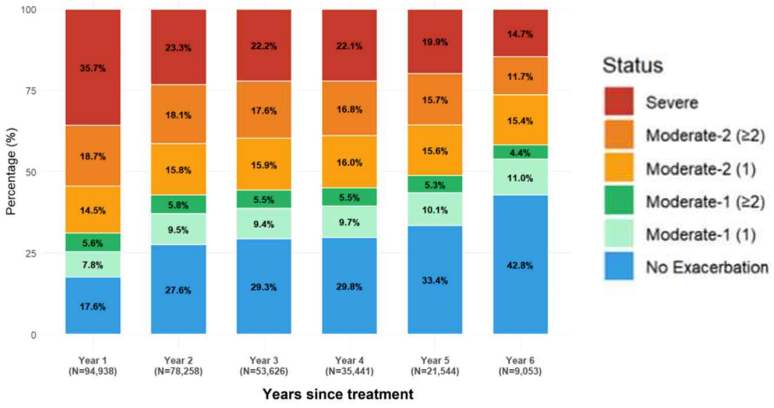
Despite Rapid Decline in Exacerbation Free Survival

Unpublisehd data

Treatment for moderate exacerbation

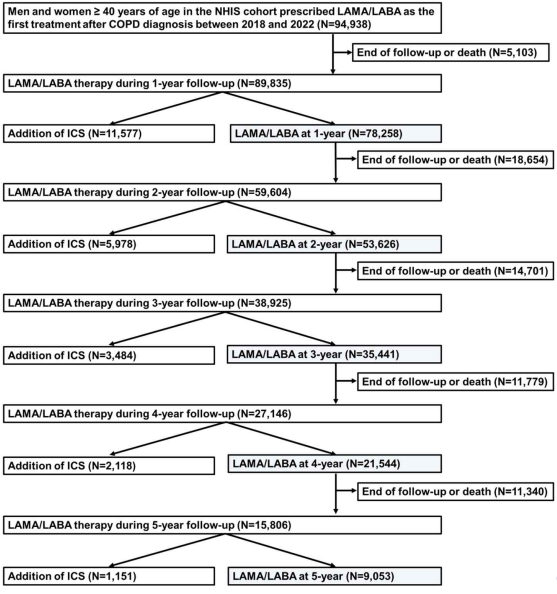
- Treated with Antibiotics alone (Moderate-1)
- Treated with Systemic corticosteroid with or without antibiotics (Moderate-2)

Among patients maintained LAMA/LABA



Unpublisehd data

Target trial emulation



Unpublisehd data

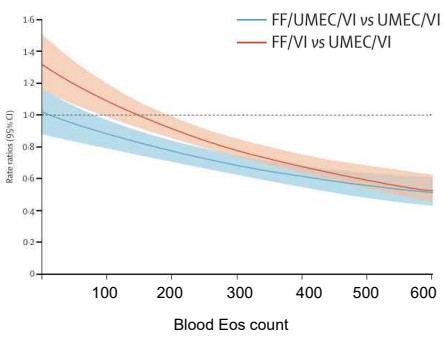
Future AE risk after one moderate AE while on LAMA/LABA

	Number of events (Incidence rate, per 100 person-year)		LAMA/LABA vs. ICS addition (reference)
	LAMA/LABA	ICS addition	HR (95% CI)
Moderate-1 exacerbation: Antibiotics only	N=1,700	N=1,700	
Moderate or Severe exacerbation	1354 (115.4)	1404 (111.7)	1.01 (0.94, 1.09)
Moderate exacerbation	1095 (71.4)	1179 (72.2)	0.98 (0.90, 1.06)
Severe exacerbation	813 (32.2)	834 (31.6)	1.02 (0.92, 1.12)
Moderate-2 exacerbation: Corticosteroid	N=4,124	N=4,124	
Moderate or Severe exacerbation	3713 (244.2)	3637 (192.5)	**1.18 (1.12, 1.23)**
Moderate exacerbation	3398 (179.1)	3317 (141.1)	**1.19 (1.13, 1.24)**
Severe exacerbation	2189 (36.9)	2064 (32.9)	**1.11 (1.04, 1.17)**

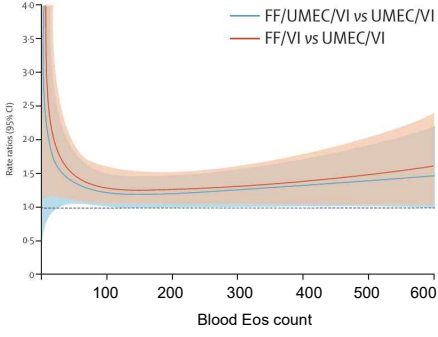
Unpublisehd data

Unclear benefit of ICS for AE treated with antibiotics only

IMPACT



AE Requiring both antibiotics and steroid



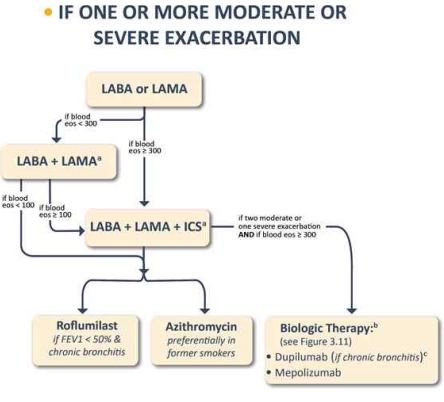
AE Requiring antibiotics only

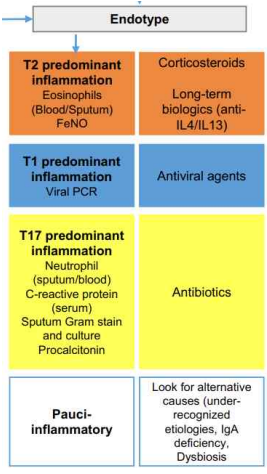
Pascoe et al. Lancet Respir Med. 2021;9(12):e114.

Beyond the exacerbation frequency alone

Treatment required during an exacerbation may serve as a pragmatic clinical surrogate for the underlying inflammatory endotype and inform subsequent therapeutic escalation strategies.

Toward the precision medicine

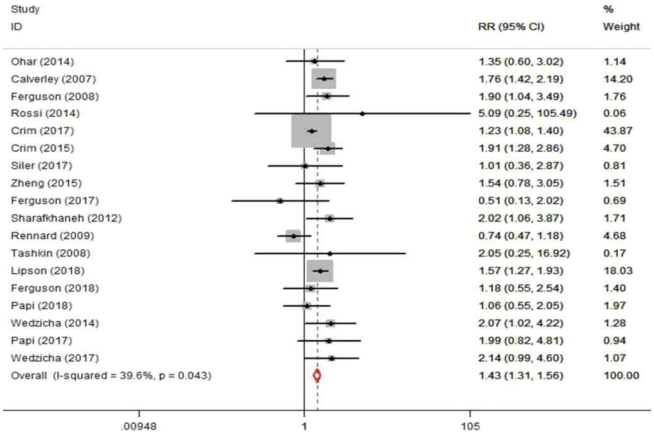




Bhatt et al. AJRCCM 2023; 208: 1026-1041.

III Concerns with ICS

Pneumonia risk with ICS



- Meta-analysis (18 RCTs)
- Pneumonia risk with ICS
  = RR 1.43 (1.31 – 1.56)

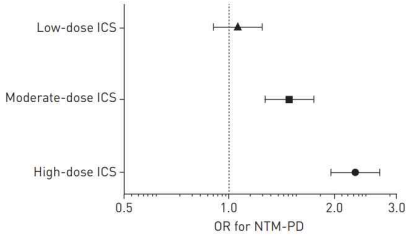
- Risk factors
  - ✓ Age > 65
  - ✓ FEV1 < 50% pred
  - ✓ Higher ICS dose
  - ✓ Longer ICS duration
  - ✓ ICS type (Fluticasone)

Zhang et al. Copd 2020; 17: 462-469.

Mycobacterial infection with ICS in OLD

- Population-based nested case-control study in Ontario, Canada
- Adults aged ≥66 years with treated obstructive lung disease → 2966 NTM-PD out of 417494 patients

	NTM-PD cases[#]	Controls[¶]	Adjusted OR* (95% CI)
All OLD			
No ICS use	592 (20.0)	4175 (35.2)	1.0 (reference)
Prior ICS use	469 (15.8)	2647 (22.3)	0.94 (0.80–1.11)
Current ICS use	1905 (64.2)	5029 (42.4)	1.86 (1.60–2.15)
Fluticasone	1576 (53.1)	3779 (31.9)	2.09 (1.80–2.43)
Budesonide	291 (9.8)	1070 (9.0)	1.19 (0.97–1.45)
Other ICS[¶]	38 (1.28)	180 (1.5)	1.29 (0.86–1.93)



Borde et al. Eur Respir J. 2017;50(3):1700037.

Other side effects with ICS in patients with COPD

Side effect	RCT	Observational Study	Systematic review
Pneumonia	✔	✔	✔
Tuberculosis		✔	
Bone fracture	(no effect)*	✔	✔
Skin thinning/easy bruising	✔		
Cataract		✔	
Diabetes	✔	✔	✔
Oropharyngeal candidiasis	✔	✔	✔

*FVI (200 μg FF) group showed increased non-traumatic Fracture.

Price et al. Prim Care Respir J 2013; 21 (1): 92-100

Summary

Single Moderate Exacerbation → Increased Risk

Uniform escalation to Triple therapy after Single Moderate AE ?

- **No proven benefit**
- **Concerns with ICS use**

Thank You

freshsun@skku.edu