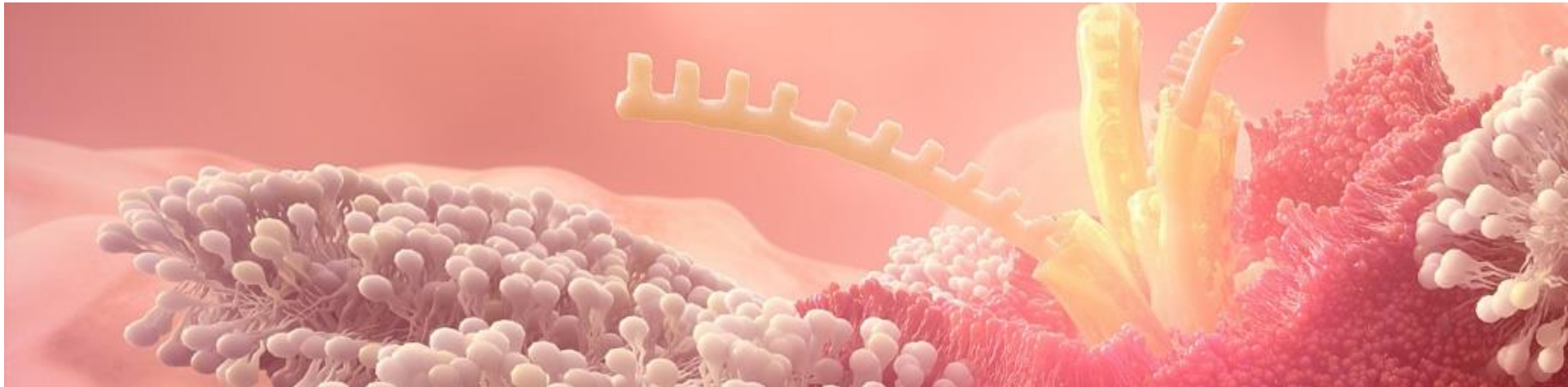


# KOL behandling anno 2023



Oktober 2023

**Anders Løkke**  
**Medicinsk afdeling, Vejle**  
**Sygehus Lillebælt**

# Potential Conflicts of Interest - Speaker Fees

**Almirall  
AstraZeneca  
BI**

**Chiesi**

**Danmarks Lungeforening  
Dansk Selskab for hjerte/lunge fysioterapi**

**DLS**

**GSK**

**Intermune**

**Medicinske Konferencer**

**Norpharma**

**Novartis**

**Nycomed/Takeda**

**Pfizer**

**Orion**

**Region H, Midt og Syd**

**Sandoz**

**Sundhedsstyrelsen**

**TEVA**



# Hvordan stiller man diagnosen KOL?

1. Kronisk luftvejsobstruktion (spirometri)

2. Relevant eksposition (Tobak/erhverv)

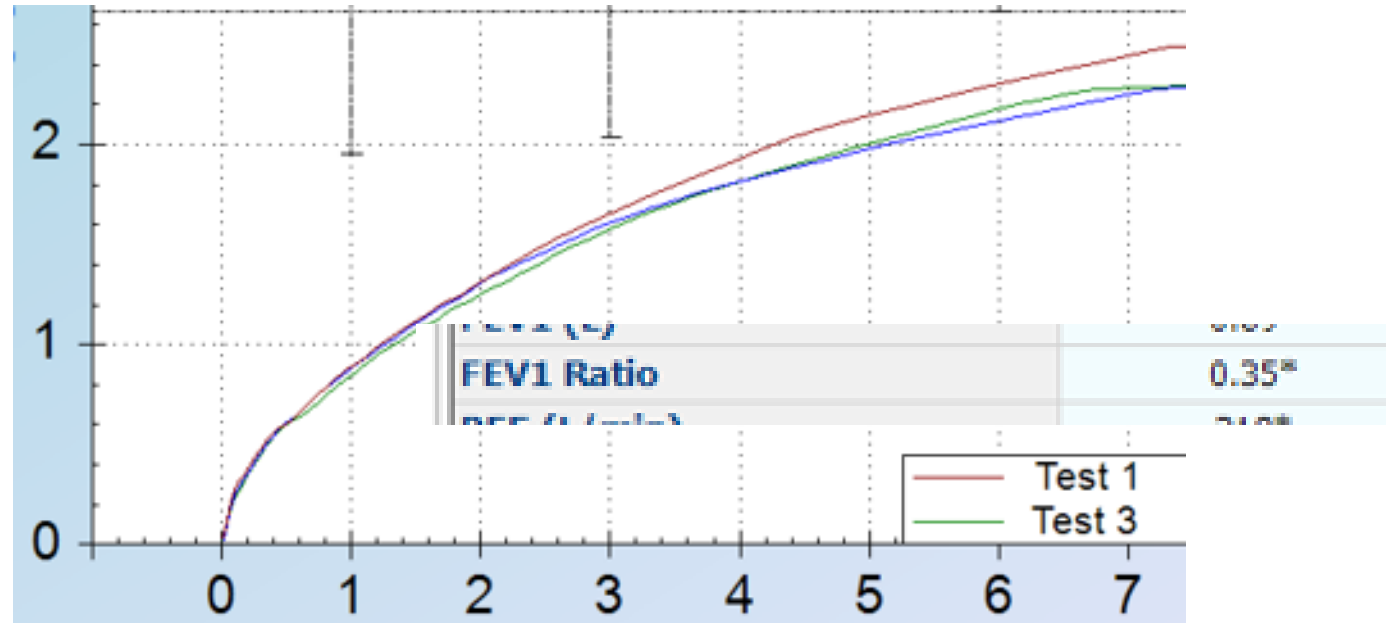
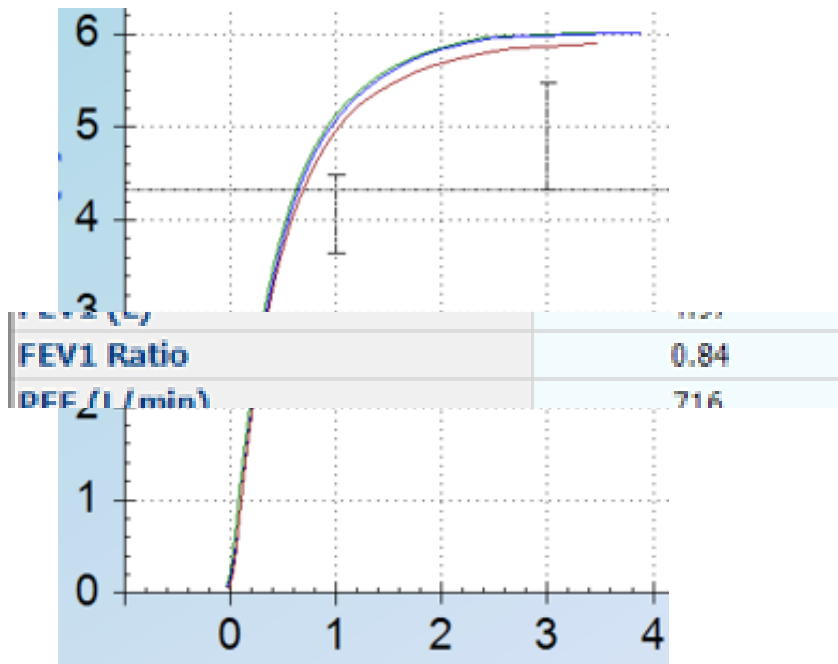
3. Symptomer

- Opsporing! (1 til 5)



# FEV1/FVC (Ratio)

- Brøken **FEV1/FVC** udregnes for at sammenligne luftvejenes åbningsgrad med lungestørrelsen = hvor meget pustes ud efter det 1. sekund i forhold til den totale mængde luft.



# Case I

**Verner – 72 år**

**Kendt med Diabetes-2, hypertension og tidl. AMI**

**Derudover tobaksinduceret KOL (eksryger)**

**Lungefunktion med FEV1 på 72%**

**MRC-åndenødsscore: 3**

**Ingen forværringer det seneste år**

**Får ingen fast inhalationsmedicin, tager Bricanyl  
pn**

**Kommer til årskontrol i almen praksis –  
vil du ændre på noget?**



# Case I

**Verner 72 år – ingen forværringer det seneste år**

**Kommer til årskontrol i almen praksis  
- vil du ændre på noget?**

- 1) Nej**
- 2) Ja – øge til LABA**
- 3) Ja – øge til LAMA**
- 4) Ja – øge til LABA og LAMA**
- 5) Ja – øge til LABA og ICS**
- 6) Ja – øge til LABA og LAMA og ICS**



# Case II

**Grethe – 72 år**

**Kendt med familiær hyperkolesterolæmi**

**Derudover tobaksinduceret KOL (eksryger)**

**Lungefunktion med FEV1 på 72%**

**MRC-åndenødsscore: 3**

**Én moderat forværringer det seneste år (tablet)**

**Får ingen fast inhalationsmedicin, tager Bricanyl  
pn**

**Kommer til årskontrol i almen praksis –  
vil du ændre på noget?**



# Case II

**Grethe 72 år – én forværring det seneste år**

**Kommer til årskontrol i almen praksis  
- vil du ændre på noget?**

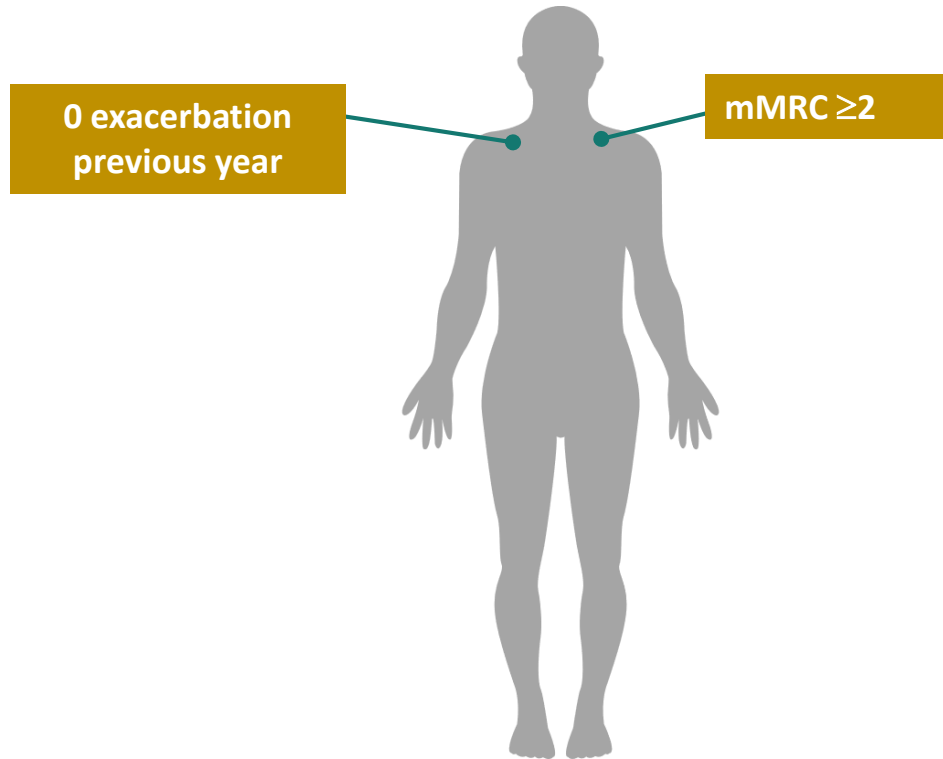
- 1) Nej**
- 2) Ja – øge til LABA**
- 3) Ja – øge til LAMA**
- 4) Ja – øge til LABA og LAMA**
- 5) Ja – øge til LABA og ICS**
- 6) Ja – øge til LABA og LAMA og ICS**



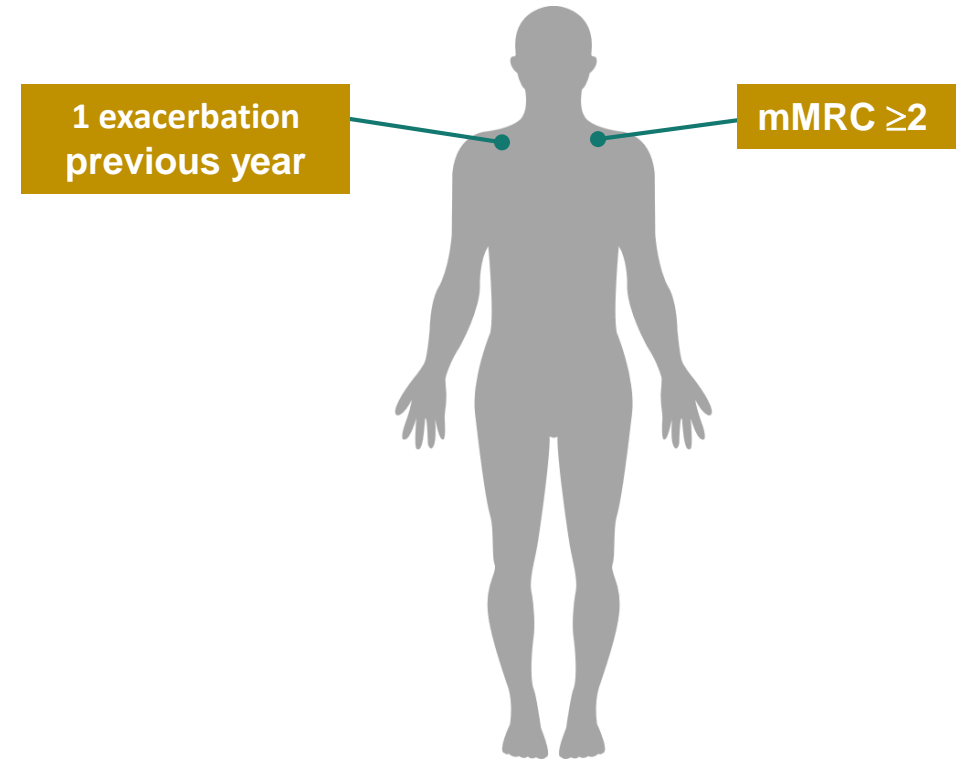


# By definition two "equal" GOLD B patients (mMRC $\geq 2$ ; 0 or 1 moderate exacerbation last 12 months)

What is the future risk for the patient?



What is the future risk for the patient?







- Does it matter if my patient has zero or 1 exacerbation for the future risk?

What is the future short and long term risk for a patient in GOLD B and does previous exacerbation status matter?



# Disease Trajectories and Impact of One Moderate Exacerbation in Gold B COPD Patients

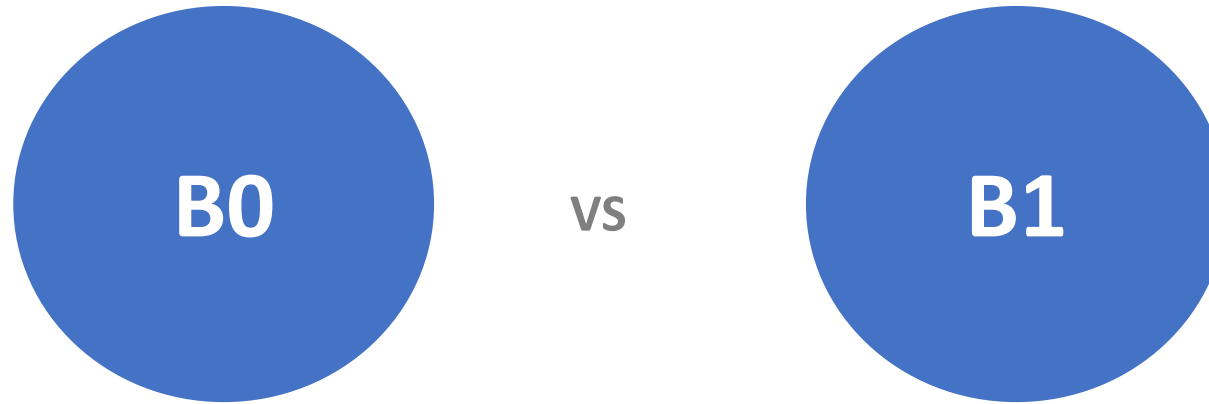
Anders Løkke <sup>1,2</sup>, Ole Hilberg<sup>1,2</sup>, Peter Lange <sup>3,4</sup>, Rikke Ibsen<sup>5</sup>, Georgios Stratelis<sup>6,7</sup>,  
Sofie de Fine Licht <sup>6</sup>, Jesper Lykkegaard <sup>8</sup>

<sup>1</sup>Department of Medicine, Little Belt Hospital, Vejle, Denmark; <sup>2</sup>Department of Regional Health Research, University of Southern Denmark, Odense, Denmark; <sup>3</sup>Medical Department, Copenhagen University Hospital-Herlev, Herlev, Denmark; <sup>4</sup>Department of Public Health, Section of Epidemiology, University of Copenhagen, Copenhagen, Denmark; <sup>5</sup>i2Minds, Aarhus, Denmark; <sup>6</sup>AstraZeneca Nordic, Södertälje, Sweden; <sup>7</sup>Department of Medical Sciences, Respiratory, Allergy and Sleep Research, Uppsala University, Uppsala, Sweden; <sup>8</sup>Research Unit for General Practice, Institute of Public Health, University of Southern Denmark, Odense, Denmark

# Methods



# Objectives



**We assessed the disease trajectory in symptomatic patients with COPD with no or one moderate exacerbation during the previous year**

# Design and Methodology

## Study design



Observational,  
population-based  
cohort study

## Data sources



Danish nationwide registries, including the COPD Registry, Patient Register, Prescribed Drug Register, CPR Register

## Study population



Patients with COPD\* aged  $\geq 40$  years treated in secondary care during 2008–2014



Patients with cancer or diagnosis of a disease requiring OCS treatment

# mMRC Symptom Score



<b>Grade</b>	<b>Description of Breathlessness</b>
Grade 0	I only get breathless with strenuous exercise
Grade 1	I get short of breath when hurrying on level ground or walking up a slight hill
Grade 2	On level ground, I walk slower than people of the same age because of breathlessness, or I have to stop for breath when walking at my own pace on the level
Grade 3	I stop for breath after walking about 100 yards or after a few minutes on level ground
Grade 4	I am too breathless to leave the house or I am breathless when dressing

# Data Sources

## Danish COPD Registry

- mMRC symptom score, FEV1, smoking status, BMI etc.

## Hospital Registry

- Hospital contacts, comorbidities

## Prescription Drug Registry

- Prescribed medication collected at pharmacy

## CPR Registry

- Vital status (dead/alive), Co-habitation





# Definition of Exacerbations



## Moderate exacerbations



Short-term use of OCS\*

## Severe exacerbations

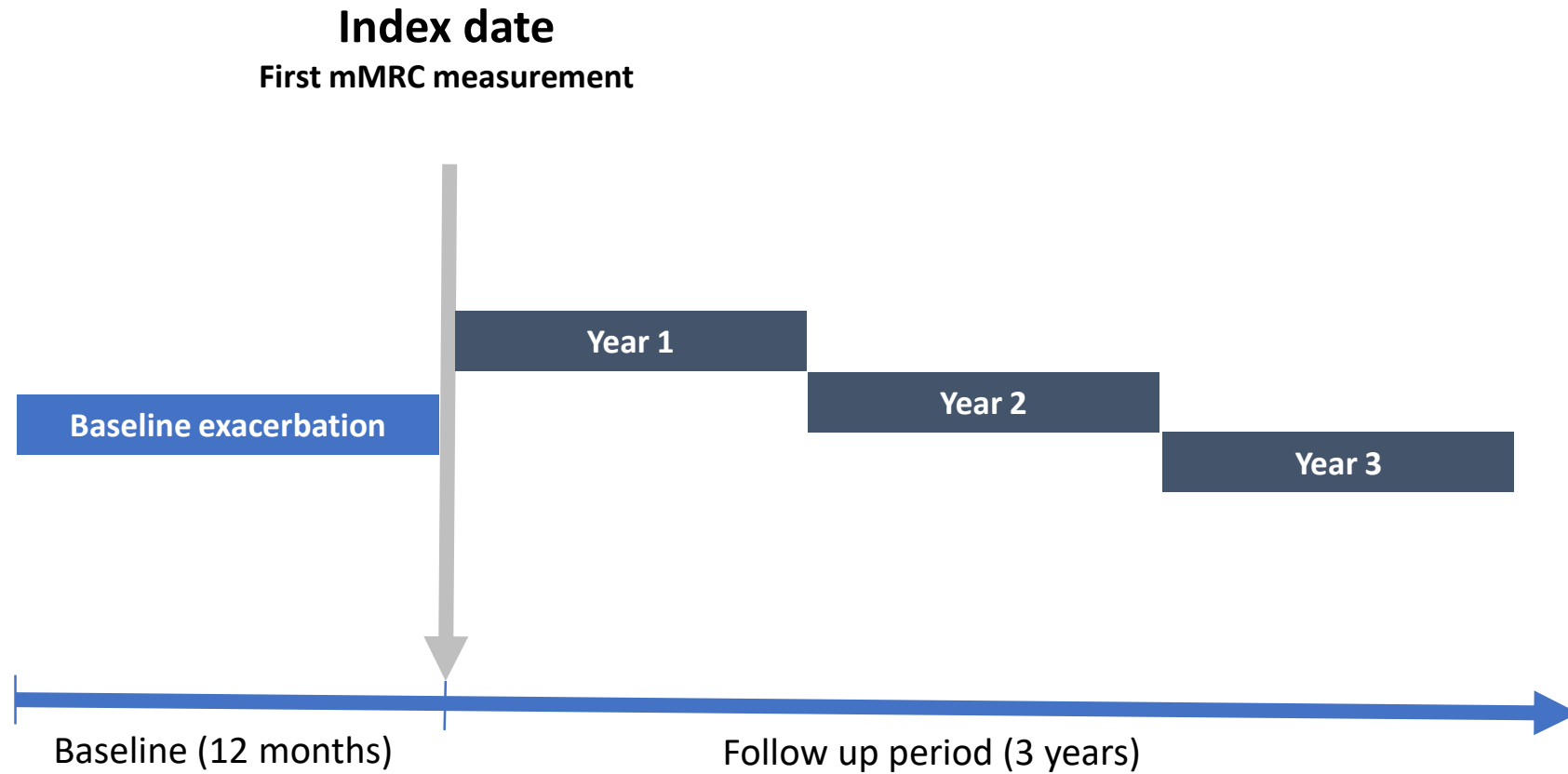


Hospital admissions or emergency room visits for COPD

\* Max 20 DDD of 25 mg prednisolone

# Study Design

Study period: 2008-2017



# Baseline characteristics

	GOLD B0		GOLD B1		P-value
	n	%	n	%	
<b>Patients</b>	4,545		3,908		
<b>Sex</b>					
Male	2,323	51.1	1,951	49.9	0.276
Female	2,222	48.9	1,957	50.1	
<b>Cohabitation status</b>					
Not cohabitating	2,398	52.8	1,918	49.1	<0.001
Cohabitating	2,147	47.2	1,990	50.9	
<b>Age (years)</b>					
Mean age (SD)	70.1 (10.2)		69.9 (10.2)		0.430
40–49	152	3.3	122	3.1	0.712
50–59	599	13.2	551	14.1	
60–69	1,264	27.8	1,100	28.1	
70–79	1,683	37.0	1,423	36.4	
80+	847	18.6	712	18.2	
<b>mMRC score</b>					
2	2,556	56.2	2,143	54.8	0.422
3	1,347	29.6	1,189	30.4	
4	642	14.1	576	14.7	

# Baseline characteristics

	GOLD B0		GOLD B1		P-value
	n	%	n	%	
<b>FEV1 (% of predicted)</b>					
80+	185	4.1	127	3.2	0.114
50–79	1,722	37.9	1,436	36.7	
30–49	1,904	41.9	1,691	43.3	
<30	734	16.1	654	16.7	
<b>BMI (kg/m<sup>2</sup>)</b>					
<18	458	10.1	380	9.7	0.879
18–24	1,609	35.4	1,373	35.1	
25–29	1,328	29.2	1,129	28.9	
30–34	728	16.0	644	16.5	
35+	422	9.3	382	9.8	
<b>Smoking status</b>					
Not current smoker	2,903	63.9	2,519	64.5	0.576
Current smoker	1,642	36.1	1,389	35.5	
<b>Baseline treatment*</b>					
No claims	1,376	30.3	966	24.7	<0.001
LAMA	561	12.3	440	11.3	
LABA	163	3.6	150	3.8	
LABA/ICS	727	16.0	709	18.1	
LABA/LAMA	211	4.6	193	4.9	
LABA/LAMA/ICS	1,507	33.2	1,450	37.1	
<b>Charlson Comorbidity Index (CCI)</b>					
Mean (SD)	0.36 (0.89)		0.36 (0.88)		0.7190

# Results



# Exacerbation pattern during each Year and Cumulated Number of Events Over All Three Years

	Year 1		Year 2		Year 3		Total Follow Up*	
	n	%	n	%	n	%	n	%
<b>GOLD B0</b> n=4545								
No exacerbations	1,996	43.9	1,785	39.3	1,477	32.5	681	15.0
1 moderate exacerbation	936	20.6	742	16.3	719	15.8	869	19.1
≥2 moderate exacerbations	502	11.0	470	10.3	398	8.8	619	13.6
≥1 Severe exacerbation	516	11.4	502	11.0	468	10.3	893	19.6
Dead	501	11.0	912	20.1	1,306	28.7	1,306	28.7
OCS censoring**	94	2.1	134	2.9	177	3.9	177	3.9
<b>GOLD B1</b> n=3908								
No exacerbations	1,284	32.9	1,110	28.4	975	24.9	321	8.2
1 moderate exacerbation	894	22.9	742	19.0	619	15.8	653	16.7
≥2 moderate exacerbations	698	17.9	588	15.0	587	15.0	774	19.8
≥1 Severe exacerbation	537	13.7	563	14.4	455	11.6	888	22.7
Dead	403	10.3	783	20.0	1,121	28.7	1,121	28.7
OCS censoring	92	2.4	122	3.1	151	3.9	151	3.9
p-value	<0.001		<0.001		<0.001		<0.001	

# Having one moderate exacerbation in the previous year increased the risk of experiencing a new moderate, severe exacerbation or death

The odds (OR) of exacerbations and death in **GOLD B1** compared to GOLD B0, per year AND all 3 Years combined<sup>a</sup>

	Year 1	Year 2	Year 3	Total Follow Up <sup>a</sup>
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
1 moderate	<b>1.48</b> (1.31–1.66)	<b>1.60</b> (1.41–1.82)	<b>1.29</b> (1.12–1.47)	<b>1.58</b> (1.33–1.87)
≥2 moderate	<b>2.13</b> (1.86–2.44)	<b>2.00</b> (1.72–2.29)	<b>2.19</b> (1.88–2.60)	<b>2.60</b> (2.19–3.08)
≥1 severe	<b>1.60</b> (1.39–1.84)	<b>1.80</b> (1.56–2.08)	<b>1.46</b> (1.25–1.70)	<b>2.08</b> (1.76–2.45)
Death	<b>1.26</b> (1.08–1.48)	<b>1.42</b> (1.24–1.62)	<b>1.32</b> (1.16–1.49)	<b>1.85</b> (1.57–2.17)

OR adjusted for age, sex, cohabitation status, comorbidity, lung function, BMI and smoking

Farmakologisk Behandling



# Inhalationsmedicin til astma og KOL

## **Luftvejsudvidende/bronkiedilaterende:**

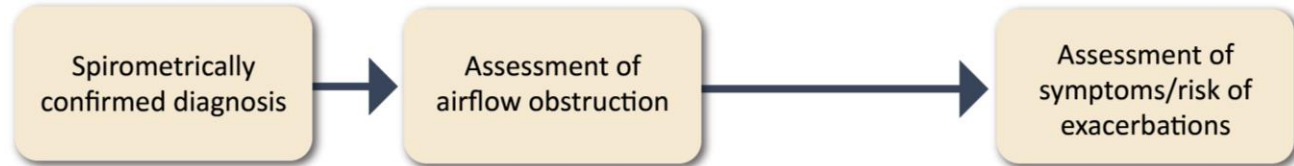
- SABA – korttidsvirkende B2 agonist
- SAMA – korttidsvirkende antikolinergika
- LABA – langtidsvirkende B2 agonist
- LAMA – langtidsvirkende antikolinergika

## **Inflammationshæmmende:**

- ICS – inhalationssteroid
- Findes i mange kombinationer og devices.
- Vær opmærksom på patientens sugekraft, og om devices kan håndteres

**GOLD ABE Assessment Tool**

Figure 2.3

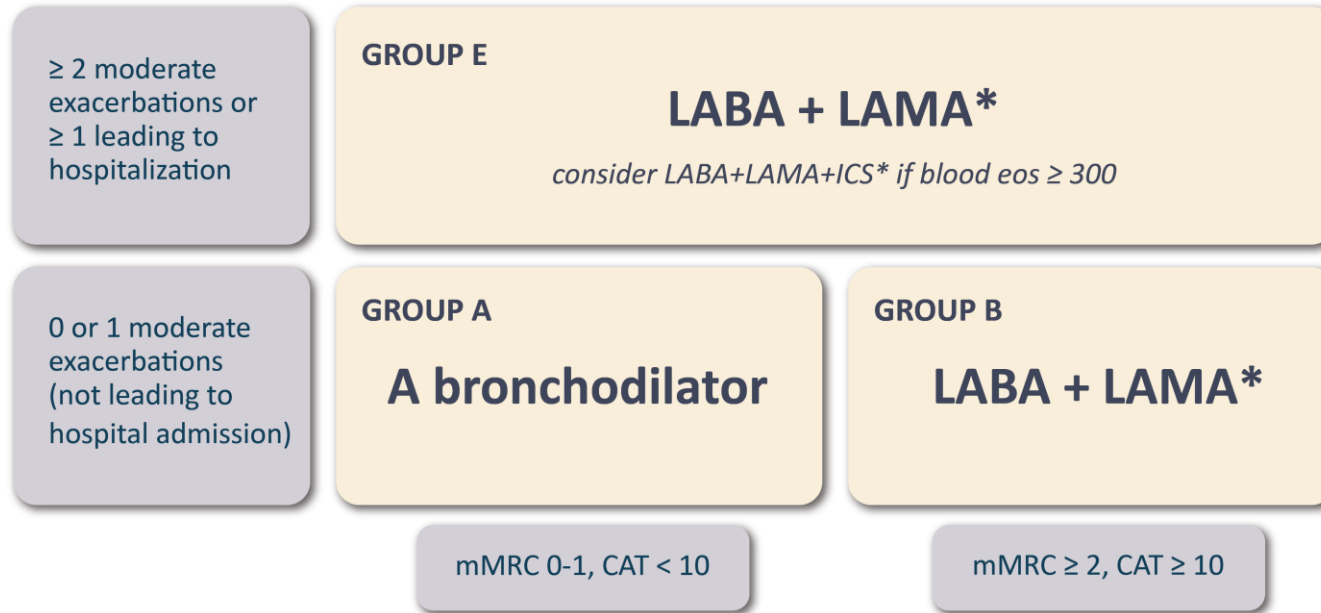


Post-bronchodilator FEV1/FVC < 0.7	GRADE		FEV1 (% predicted)	EXACERBATION HISTORY (PER YEAR)		SYMPTOMS	
	<b>GOLD 1</b>		≥ 80	≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization		<b>E</b>	
	<b>GOLD 2</b>		50-79	0 or 1 moderate exacerbations (not leading to hospitalization)		<b>A</b>	<b>B</b>
	<b>GOLD 3</b>		30-49			mMRC 0-1 CAT < 10	mMRC ≥ 2 CAT ≥ 10
<b>GOLD 4</b>		< 30					



## Initial Pharmacological Treatment

Figure 4.2

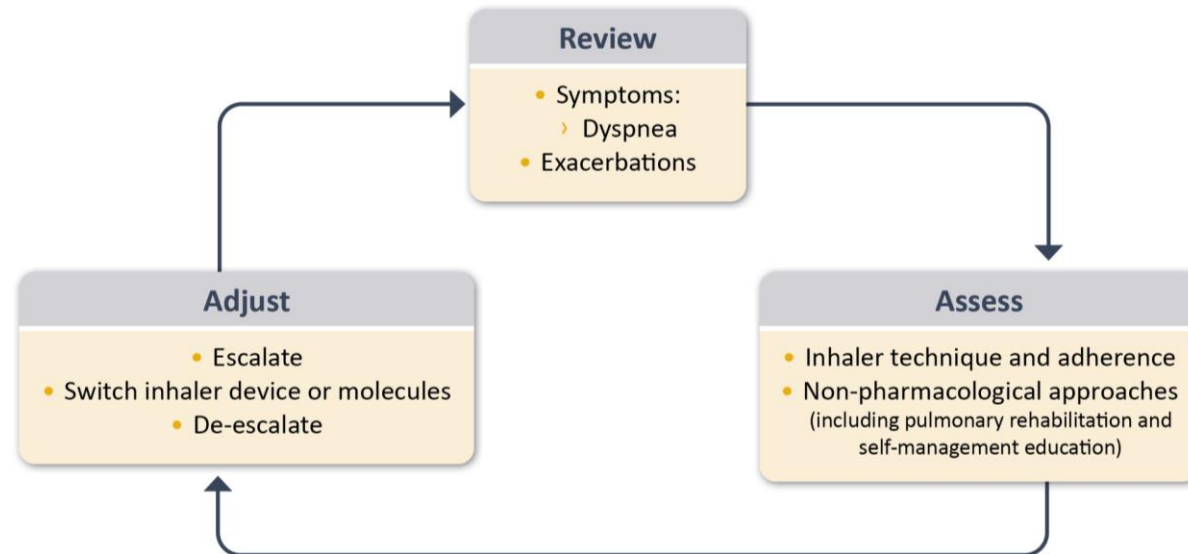


\*single inhaler therapy may be more convenient and effective than multiple inhalers  
Exacerbations refers to the number of exacerbations per year



## Management Cycle

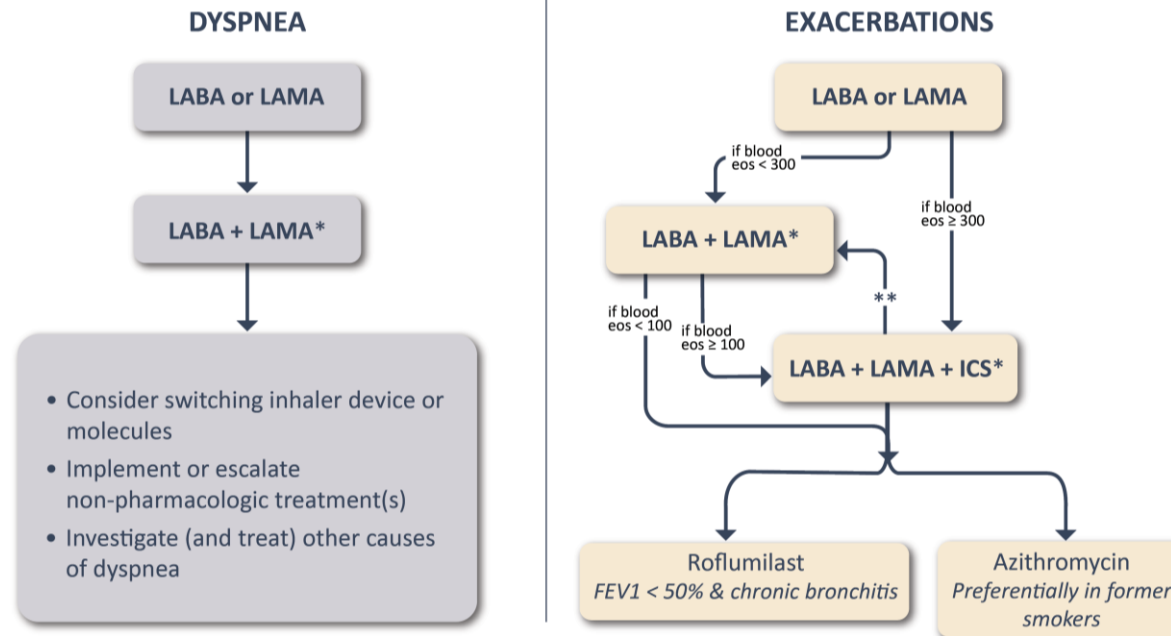
Figure 4.3



## Follow-up Pharmacological Treatment

Figure 4.4

- 1 IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.
- 2 IF NOT:
  - Check adherence, inhaler technique and possible interfering comorbidities
  - Consider the predominant treatable trait to target (dyspnea or exacerbations)
    - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
  - Place patient in box corresponding to current treatment & follow indications
  - Assess response, adjust and review
  - These recommendations do not depend on the ABE assessment at diagnosis



\*Single inhaler therapy may be more convenient and effective than multiple inhalers

\*\*Consider de-escalation of ICS if pneumonia or other considerable side-effects. In case of blood eos  $\geq 300$  cells/ $\mu$ l de-escalation is more likely to be associated with the development of exacerbations

Exacerbations refers to the number of exacerbations per year



# DSAM

Patientkarakteristik			Ikke-farmakologisk			Farmakologisk	
	Eksacerb./år	MRC	Essentielt	Anbefal	Vaccination	Førstevalg Alle SABA pn	Andet valg Alle SABA pn
<b>A – Stabil</b> Få symptomer	≤ 1	1-2*	Rygestop	Fysisk aktivitet	Influenza Pneumokok	<b>Ingenting fast</b> <sup>2</sup>	LABA
<b>B – Stabil</b> Stabil Mange symptomer		≥ 3	Rygestop og Lungerehabilitering <sup>1</sup>			<b>LABA</b>	LAMA eller LABA+LAMA
<b>C –</b> Eksacerbationer Få symptomer	≥ 2 eller 1 indlæggelse med KOL eksacerbation	1-2*				<b>LAMA</b> <sup>3</sup>	LABA+LAMA <sup>4</sup>
<b>D –</b> Eksacerbationer Mange symptomer		≥ 3	<b>LABA+LAMA</b> <sup>4</sup>			LABA+LAMA+ICS	

**SABA** = Short acting beta2-agonist (korttidsvirkende beta2-agonist)

**LABA** = Long acting beta2-agonist (langtidsvirkende beta2-agonist)

**LAMA** = Long acting muscarine antagonist (langtidsvirkende anticholinergika)

**ICS** = Inhaled corticosteroids (inhaleret kortikosteroid)

\* Overvej rehabilitering ved muskelsvækkelse og udred for mulig anden årsag/sygdom

<sup>1</sup> KOL rehabilitering i henhold til lokalt forløbsprogram

<sup>2</sup> Ved hyppig eller dagligt behov for SABA opstart LABA

<sup>3</sup> Ved flere eksacerbationer vælg LABA+LAMA

<sup>4</sup> Ved flere eksacerbationer trods LABA+LAMA tillæg ICS dvs LABA+LAMA+ICS

Har patienten også astma skal der gives ICS

# KOL-”værktøjskasse”

## Farmakologisk

- Inhalationsmedicin:
  - SABA/SAMA
  - LABA
  - LAMA
  - ICS/LABA
  - LABA/LAMA
  - LABA/LAMA/ICS
- Tabletter:
  - Antibiotika
  - Prednisolon
  - Mukolytika
  - Teo / PD4-hæmmer

## Non – farmakologisk

- Rygestop
  - Evt. hjælp fra farmaka (NRT og Cytisin)
- ”Egenomsorg”
  - Teknikker
  - Selvbehandling
  - Angsthåndtering
- Rehabilitering
- Ilt (evt. ifbm. træning)
- NIV
- Sjældent: ventiler/kirurgi

# Rygeophør

<b>Effekt af rådgivning alene</b>	<b>Rådgivning plus NRT</b>	<b>Rådgivning plus Bupropion</b>	<b>Rådgivning plus Vareniclin</b>
<b>10 %</b>	<b>20 %</b>	<b>20 %</b>	<b>30 %</b>

Andelen af patienter, som ophører tobaksrygning



# Strategier for valg af inhalationsdevice

## Keep it simple!

- Opgiv overblikket!
- Udvalg nogle få inhalatorer, som du/personalet er helt fortrolig med!
  
- Sørg for at have alle 3 typer medicin  
(LABA, LAMA og ICS), som både spray og pulver:
  
- En-gangs doseret
  
- To-gangs doseret

# Farmakologisk behandling af stabil KOL

Trin	Behandlingsforslag
1	LAMA (LABA)
2	LABA og LAMA
3	LABA og LAMA og ICS

- **Trin 1** – gives til patienter med:
  - Få symptomer (MRC 1-2) – ingen eksacerbation/indlæggelse
- **Trin 2** – gives til patienter med:
  - Mange symptomer (MRC  $\geq$  3) og/eller  $\geq$  1 årlig eksacerbation/indlæggelse
- **Trin 3** – gives til patienter der:
- På trods af behandling med LABA og LAMA (eller LABA og ICS ved ACO) har fortsatte symptomer og/eller gentagne eksacerbationer/indlæggelser

# Korttidsvirkende

- Gives som udgangspunkt ikke til nogen!
- Kan anvendes, hvis man i forvejen får maksimal behandling (LABA+LAMA), og fortsat har symptomer
- Gives KLART bedst via spacer – alternativt forstøver
  - (psykologiske aspekter)
- OBS! Bivirkninger!!!

# Virkninger

- Inhalationsbehandling bør KLART foretrækkes frem for systemisk administration (lokal effekt – i vid udstrækning atoksisk)
- **Beta-2 agonister:**
  - Afslapper den glatte muskulatur, så luftvejene udvides
  - Effektiv i ca. 2-24 timer (stor individuel variation samt mulig tilvænning)
- **Antikolinergika:**
  - Forhindrer, at luftvejene trækker sig sammen igen
  - Effektiv i ca. 2-24 timer (stor individuel variation samt mulig tilvænning)
- NB! Effekten forskellig (indhold, inhalator, formulering)

# Bivirkninger

- **Beta-2 agonister:**
  - Hyppigst ses tremor og muskelkramper samt irritation i mund og svælg
- **Antikolinergika:**
  - mundtørhed, svækket syn, obstipation, urinretention m.m.
- NB! Frekvensen forskellig (indhold, inhalator, formulering)
- Ikke farligt, **men**....det skal gerne gå godt på grund af - og ikke på trods af - behandlingen!

# Fixed dose triple treatment for COPD

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD

David A. Lipson, M.D., Frank Barnhart, D.V.M., Noushin Brealey, M.D., Jean Brooks, M.Sc., Gerard J. Criner, M.D., Nicola C. Day, Ph.D., Mark T. Dransfield, M.D., David M.G. Halpin, M.D., MeiLan K. Han, M.D.,

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD

Klaus F. Rabe, M.D., Ph.D., Fernando J. Martinez, M.D., Gary T. Ferguson, M.D., Chen Wang, M.D., Ph.D., Dave Singh, M.D., Jadwiga A. Wedzicha, M.D., Roopa Trivedi, M.S., Earl St. Rose, M.S., Shaila Ballal, M.S., Julie McLaren, M.D., Patrick Darken, Ph.D., Magnus Aurivillius, M.D., Ph.D., Colin Reisner, M.D., and Paul Dorinsky, M.D., for the ETHOS Investigators\*

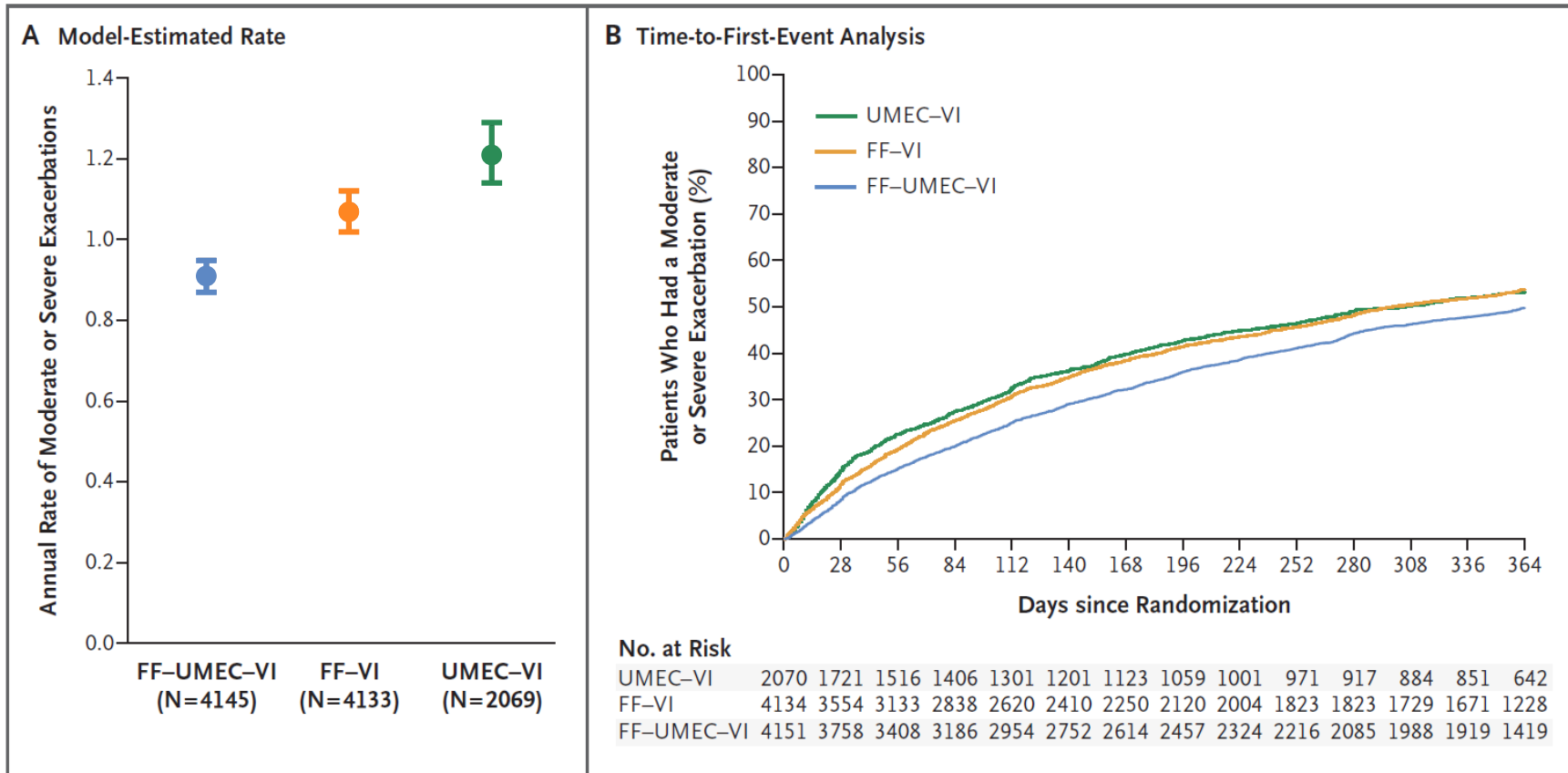
## Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease a double-blind, parallel group, randomised controlled trial

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\*

1. Lipson et al AJRCCM 2020;201:1508-16
2. Rabe KF et al. Article and supplementary appendix. N Engl J Med. 2020
2. Papi et al. Lancet . 2018 Mar 17;391(10125):1076-1084.

# Exacerbation effect of fixed dose triple treatment vs. LABA/LAMA and ICS/LABA

In the 12-month study (IMPACT), **FF/UMEC/VI** demonstrated:



**25%** risk reduction of moderate or severe COPD exacerbations vs LABA/LAMA,  $p < 0.001$

**15%** risk reduction of moderate or severe COPD exacerbations vs ICS/LABA,  $p < 0.001$

Figure 1, Lipson et al. 2018

# Exacerbation effect of fixed dose triple treatment vs. LABA/LAMA and ICS/LABA (ETHOS trial)

In the 12-month study (ETHOS), **BUD/GLY/FORM** demonstrated:

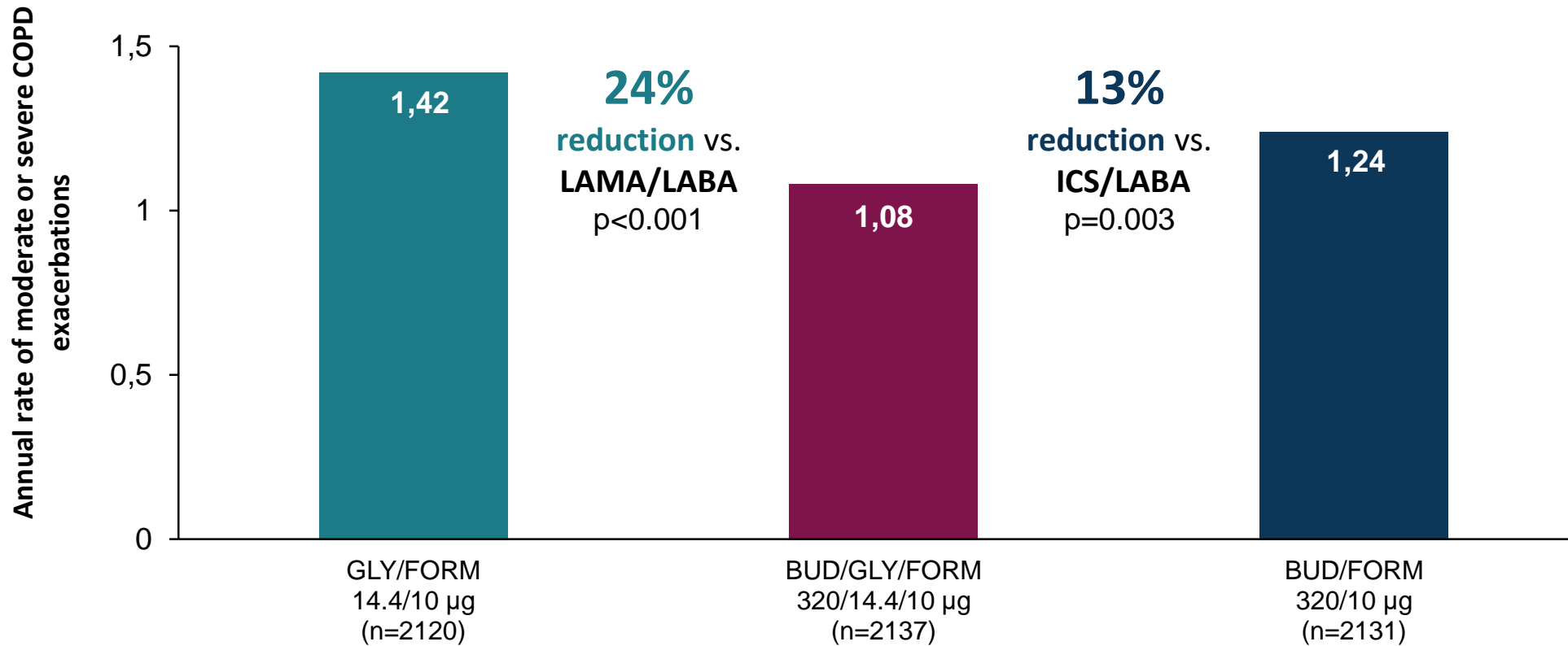


Figure adapted after Rabe et al 2020



# Fixed dose triple treatment and mortality (IMPACT)

Time to all-cause mortality (on/off treatment)

Secondary endpoint

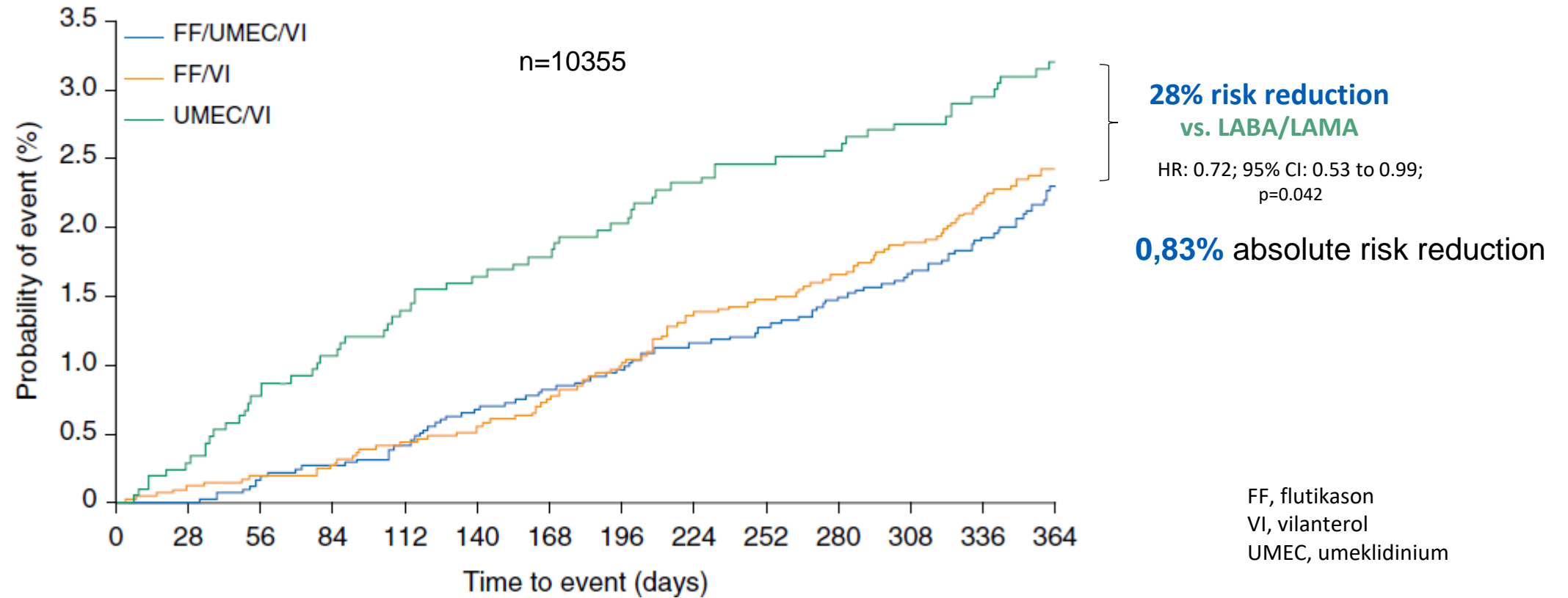


Figure 1, Lipson et al. 2020

# Fixed dose triple treatment and mortality (ETHOS)

Time to all-cause mortality (ITT population)  
Secondary endpoint

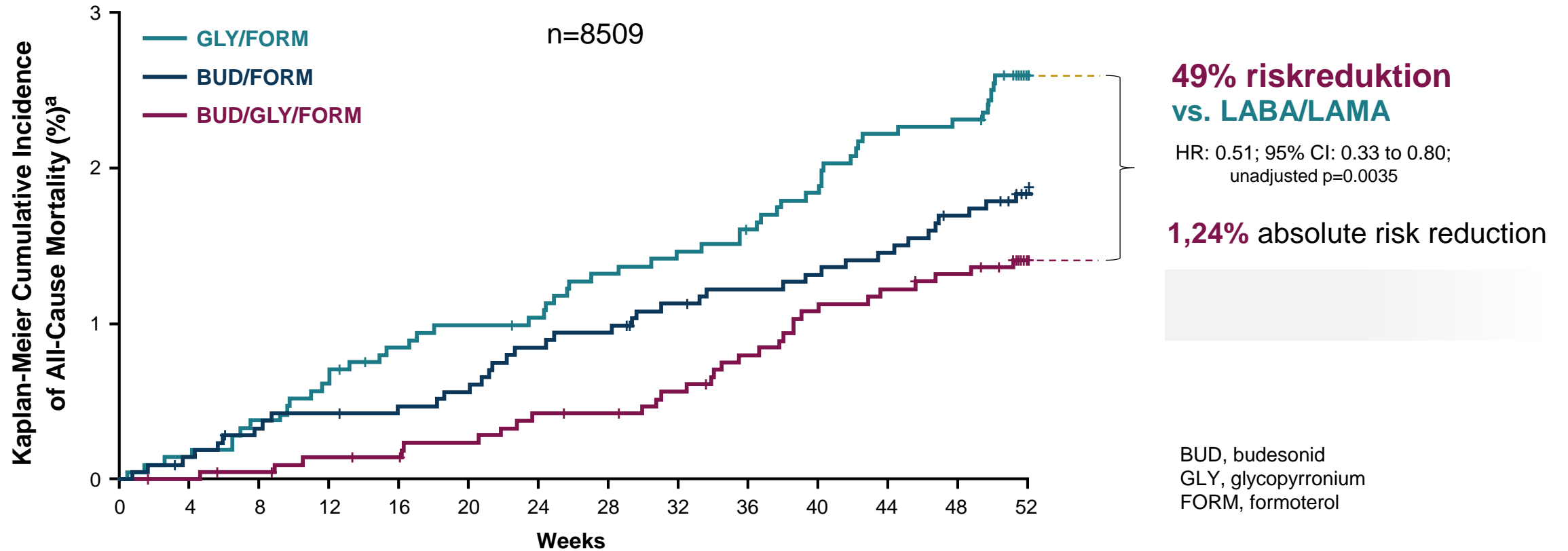
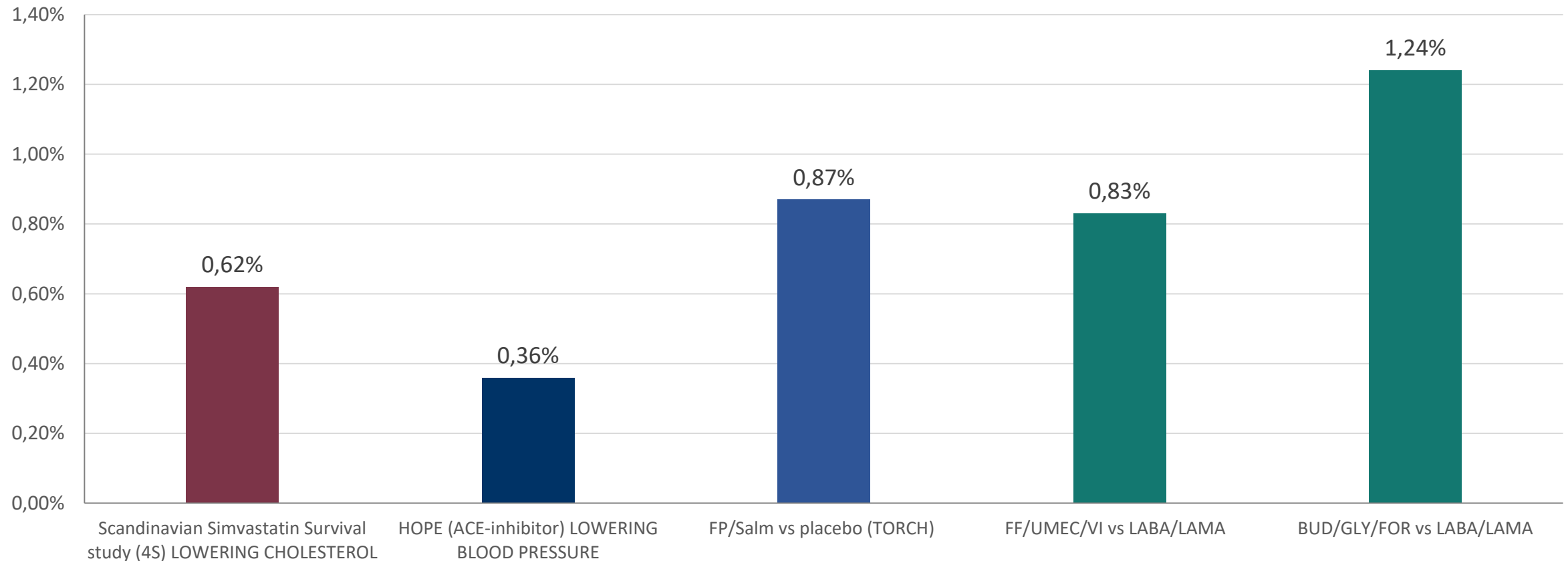


Figure adapted from Rabe KF et al. 2021

# Effect on all cause mortality in intervention studies in different disease areas

## Estimated annual **absolute risk reduction** of all cause mortality



FP, Flutikasonpropionat; SAL, Salmeterol; FF, Flutikasonfuroat; UMEC, Umeklidinium; VI, Vilanterol; BUD, Budesonid; GLY, Glykopyrronium; FOR, Formoterol

# Anvendelse af ICS

- Ved symptomer:
  - Gives i 3 måneder.
  - Vurder effekt og behandlingsindikation (+)
- Ved forværringer:
  - Gives som udgangspunkt i mindst 6-12 mdr.
  - Højt eosinofil-tal ( $>0,30$ )
  - NB! Husk altid på hvad udgangspunktet er?!

# Anvendelse af eosinofile

- Når diagnosen stilles og behandlingen skal startes op
  - hvis eosinofile er høje ( $>0,30$ ) kan behandling med ICS+LABA overvejes
- Når behandlingen med ICS skal ned/udtrappes - hvis eosinofile er høje ( $>0,30$ ) kan fortsat behandling med ICS+LABA overvejes (lav/middel dosis)

## Factors to Consider when Initiating ICS Treatment

Figure 3.1

### Factors to consider when adding ICS to long-acting bronchodilators:

(note the scenario is different when considering ICS withdrawal)

#### STRONGLY FAVORS USE

History of hospitalization(s) for exacerbations of COPD<sup>#</sup>

≥ 2 moderate exacerbations of COPD per year<sup>#</sup>

Blood eosinophils ≥ 300 cells/ $\mu$ L

History of, or concomitant asthma

#### FAVORS USE

1 moderate exacerbation of COPD per year<sup>#</sup>

Blood eosinophils 100 to < 300 cells/ $\mu$ L

#### AGAINST USE

Repeated pneumonia events

Blood eosinophils < 100 cells/ $\mu$ L

History of mycobacterial infection

<sup>#</sup>despite appropriate long-acting bronchodilator maintenance therapy (see Table 3.4 and Figure 4.3 for recommendations);

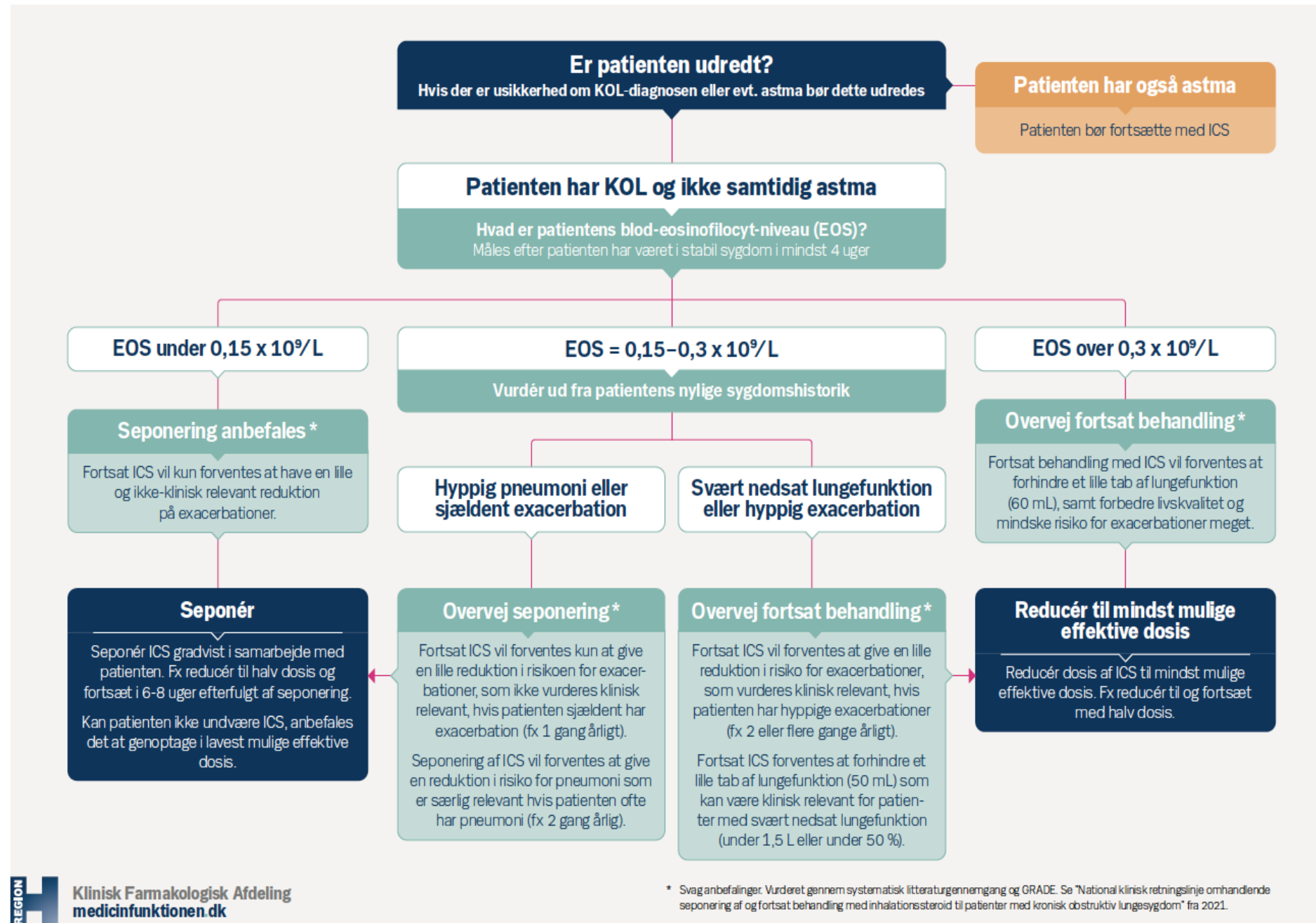
\*note that blood eosinophils should be seen as a continuum; quoted values represent approximate cut-points; eosinophil counts are likely to fluctuate.

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# Seponering af inhalationssteroid (ICS) hos patienter med kronisk obstruktiv lungesygdom (KOL)

– en evidensbaseret algoritme



# Spørgsmål?

