CO-DEVELOPED SYMPOSIUM

Living Longer Lives? The Role of Exacerbation Reduction on Mortality in Patients Living with COPD

Presenter: Dr. J. Alberto Neder

Moderator: Dr. Erika Penz

AstraZeneca

Living Longer Lives?
The role of exacerbation reduction on mortality in patients living with COPD

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SOCIÉTÉ CANADIENNE DE THORACOLOGIE

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Disclosure of Conflict of Interest
(over the past 2 years)

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April 7 – 9, 2022

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Disclosure of Conflict of Interest
(over the past 2 years)

Mitigating potential bias

- **The sponsor did not influence or review the content of this presentation**

- **Comprehensive updated literature review**

- **Focus on clinically-relevant data**

Canadian Respiratory Conference
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CanMEDs Roles

This session will address the following CanMEDs roles:
(Please include all that apply)

- Medical Expert (the integrating role) - X

- Communicator

- Collaborator

- Leader

- Health Advocate - X

- Scholar - X

- Professional - X

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Learning Objectives

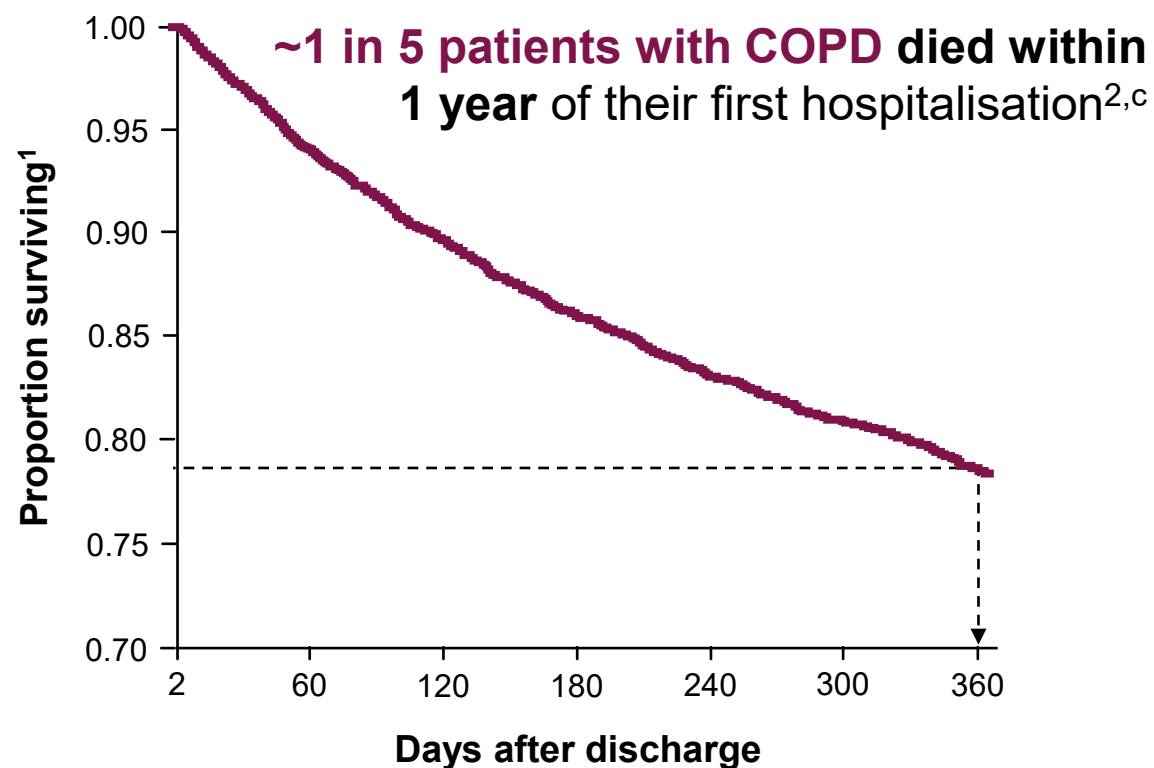At the end of this session, participants will be able to:

- **Describe the relationship between exacerbations and increased mortality risk (including CV risk)**

- **Identify patients at risk for exacerbations, and examine clinical practice approaches to improving their quality of life**

- **Discuss emerging data to support the use of triple therapies to reduce all-cause mortality**

Why do COPD patients who exacerbate die earlier?
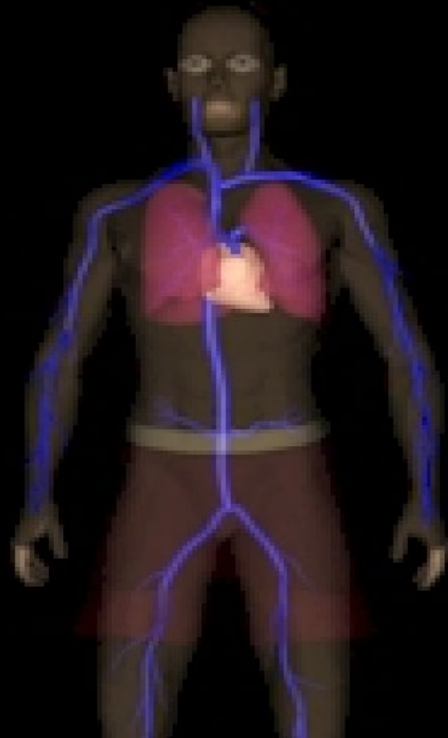
Exacerbations are associated with increased all-cause mortality

2 Moderate Exacerbations[ab] Within 1 Year Increased Risk of Death by 80% [Adjusted OR 1.80 (95% CI 1.19, 2.70)][1]

~1 in 5 patients with COPD died within 1 year of their first hospitalisation[2,c]

Proportion surviving[1] vs Days after discharge

Another study found that **respiratory** and **CV disorders** were the **most frequent causes of death** within 1 year of an exacerbation[3,d]

52%   **~20%**

Note: Figure adapted from Ho TW et al. *PLoS ONE*. 2014;9:e114866; [a]Moderate exacerbations defined as those managed outside hospital, and severe exacerbations as those requiring hospitalization; [b]based on adjusted ORs for comparison of exacerbation frequency in the prior 12 months versus those with no exacerbations in the prior 12 months during a cohort study; [c]A population-based cohort study in 4204 patients with COPD who had their first-ever exacerbation requiring hospitalization was conducted to describe the in-hospital and 1-year outcomes from the LHID in Taiwan; [d]Exacerbation requiring hospitalization. 1. Rothnie KJ et al. *Am J Respir Crit Care Med*. 2018;198:464–471.; 2. Ho TW et al. *PLoS ONE*. 2014;9:e114866; 3. Garcia-Sanz MT et al. *J Thorac Dis* 2017;9:636-645.

8
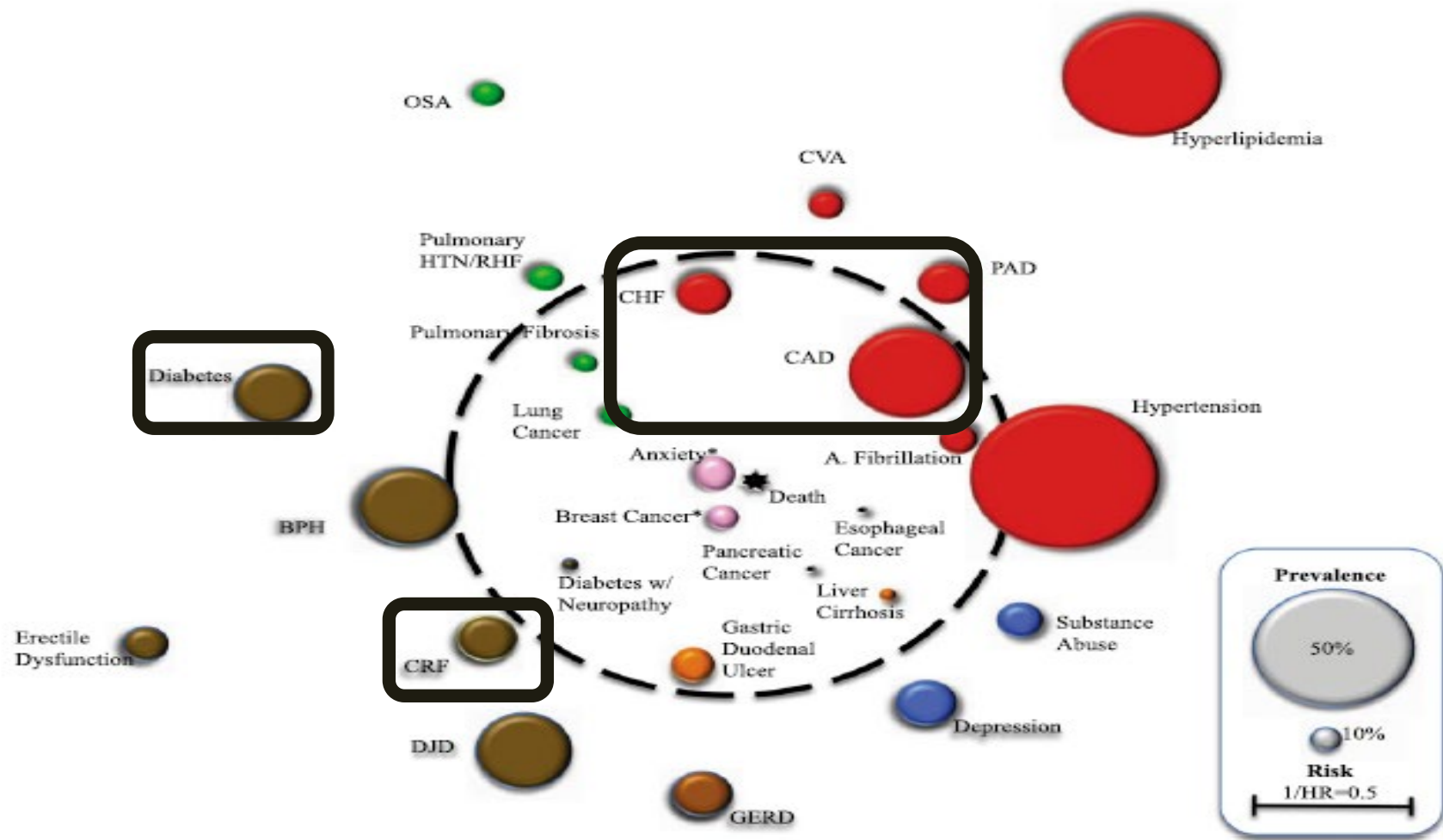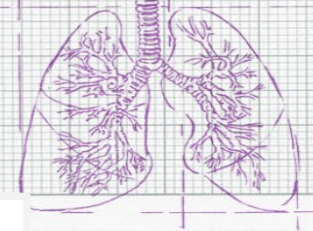
Patients with comorbid conditions are at increased risk of having frequent exacerbations

Comorbid conditions[a]
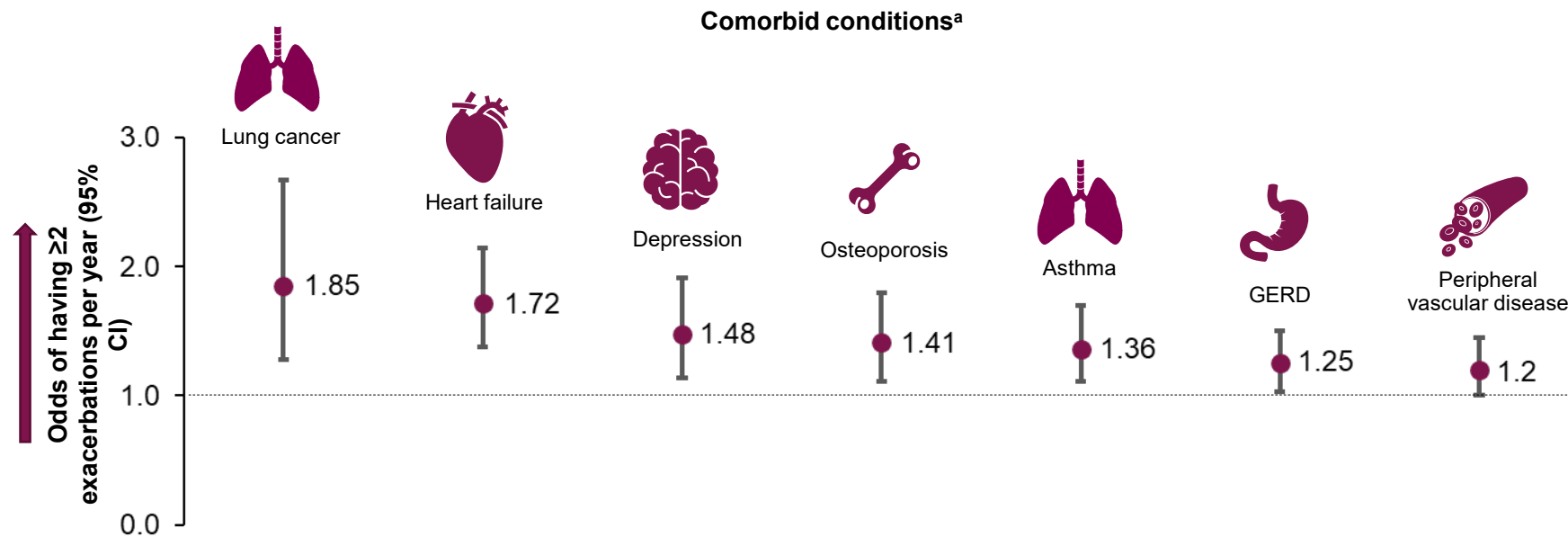
[a]Retrospective cohort study based on 2012-2013 electronic health records from 179 Dutch general practices (n=14,603); selected comorbidities associated with ≥2 exacerbations per year versus <2 exacerbations per year in patients with COPD, corrected for age and sex. Westerik JA et al. *Respir Res*. 2017;18:31.

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The impact of an exacerbation goes beyond the lungs

CV events increase in the **first 10 days** following **a moderate exacerbation**[1,a]

Legend: ■ MI ■ Stroke

Y-axis: **Incidence rate ratios**[1,a]

- 1–5 days: MI = 2.27, Stroke = 0.55
- 6–10 days: MI = 1.74, Stroke = 1.40

2x increased risk of MI[b]

40% increased risk of stroke

X-axis: **Days following a moderate COPD exacerbation**[1,c]
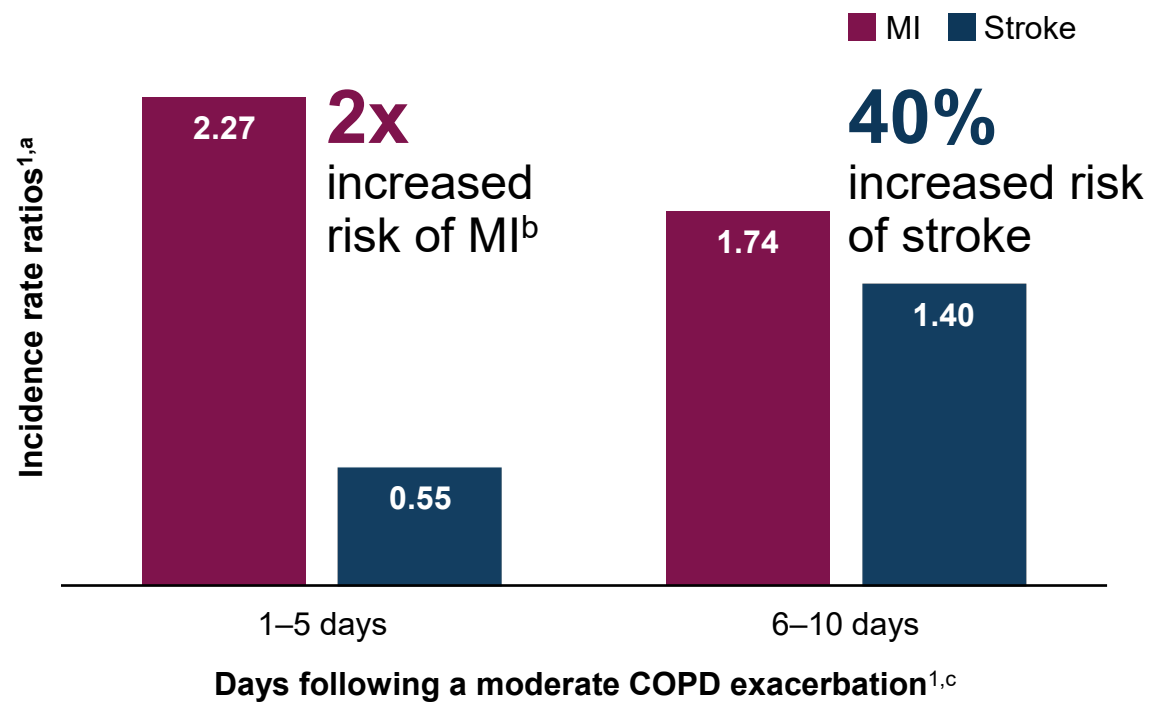
The impact of an exacerbation goes beyond the lungs

CV events increase in the **first 10 days** following **a moderate exacerbation**[1,a]

And the **risk of CV events** persists **for up to a year** after an exacerbation[2,d]

■ MI ■ Stroke

Incidence rate ratios[1,a]

2.27

2x increased risk of MI[b]

0.55

1.74

40% increased risk of stroke

1.40

1–5 days

6–10 days

Days following a moderate COPD exacerbation[1,c]
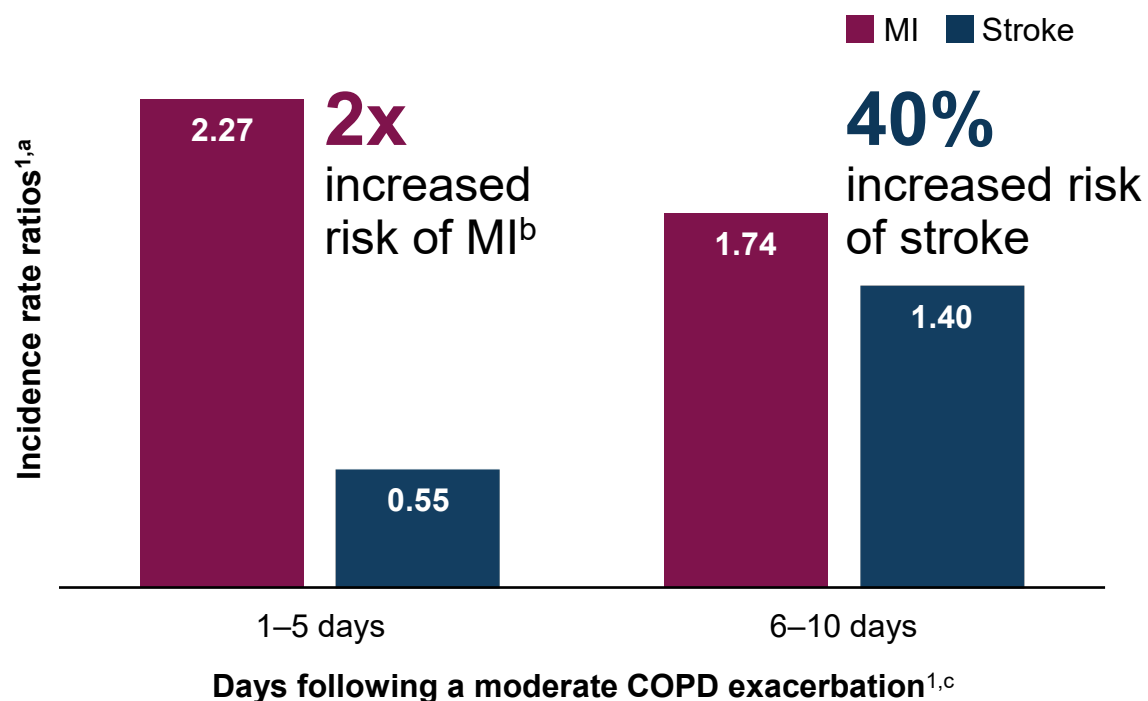
~4x risk in the **first 30 days**

90% increase from day 91 to a year

CV events consisted of CV death, MI, stroke, unstable angina, and transient ischemic attack[2]

CV comorbidities in patients with COPD significantly increases risk of death

The presence of CV comorbidities increases the **risk of mortality** in patients with COPD[1,a]

% increase in mortality risk[1,a]

COPD + ischemic heart disease

27–50% ⬆

COPD + atrial fibrillation

56% ⬆

versus COPD alone

54–70% ⬆

COPD + diabetes

30–90% ⬆

COPD + heart failure
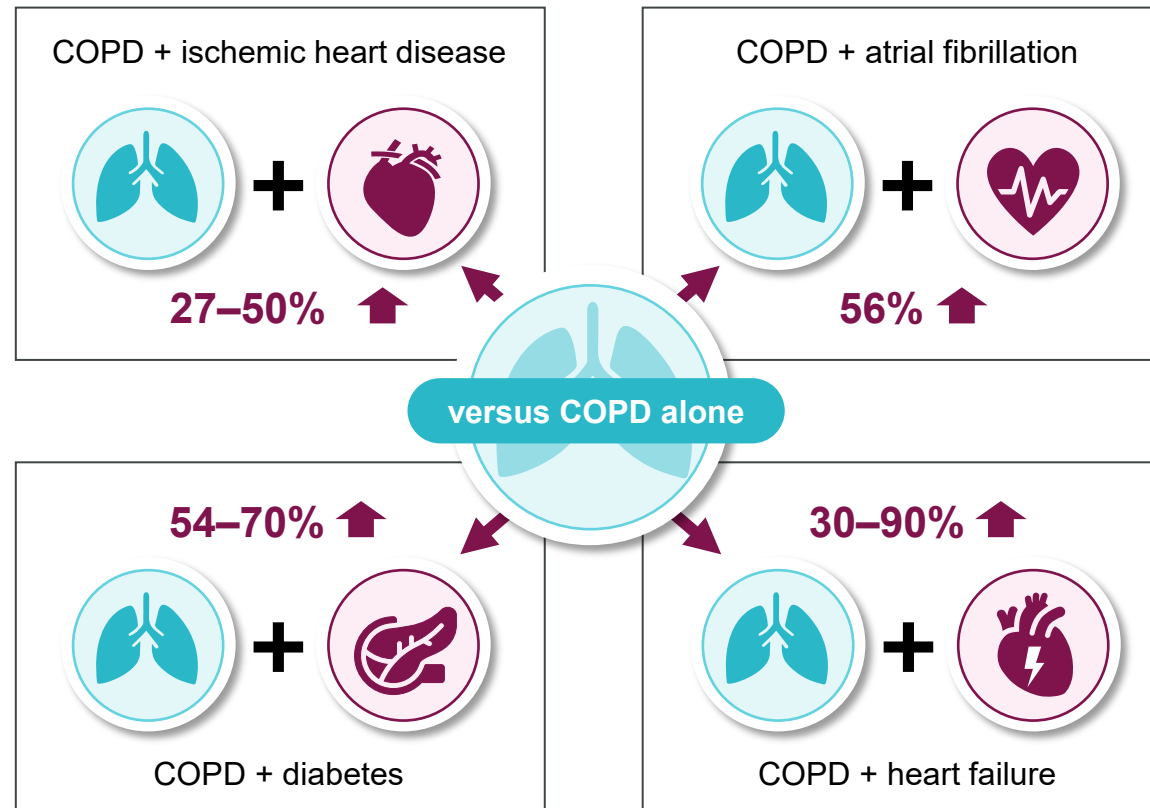
[a]data show risk of mortality for patients with COPD and each comorbidity versus COPD alone

1. Rabe K et al. *Eur Respir Rev*. 2018;27:180057.

COPD *per se* affects cardiac function !
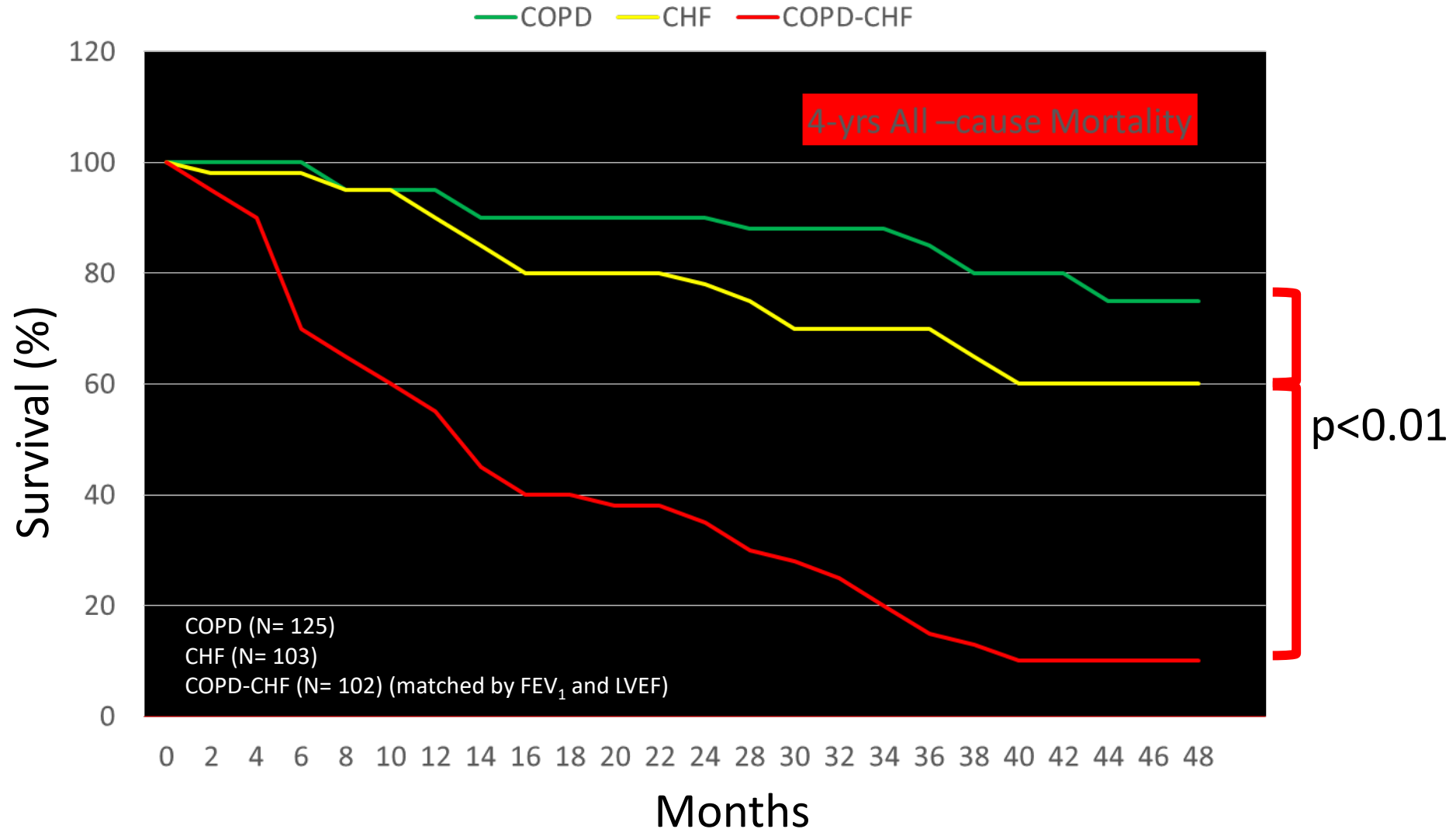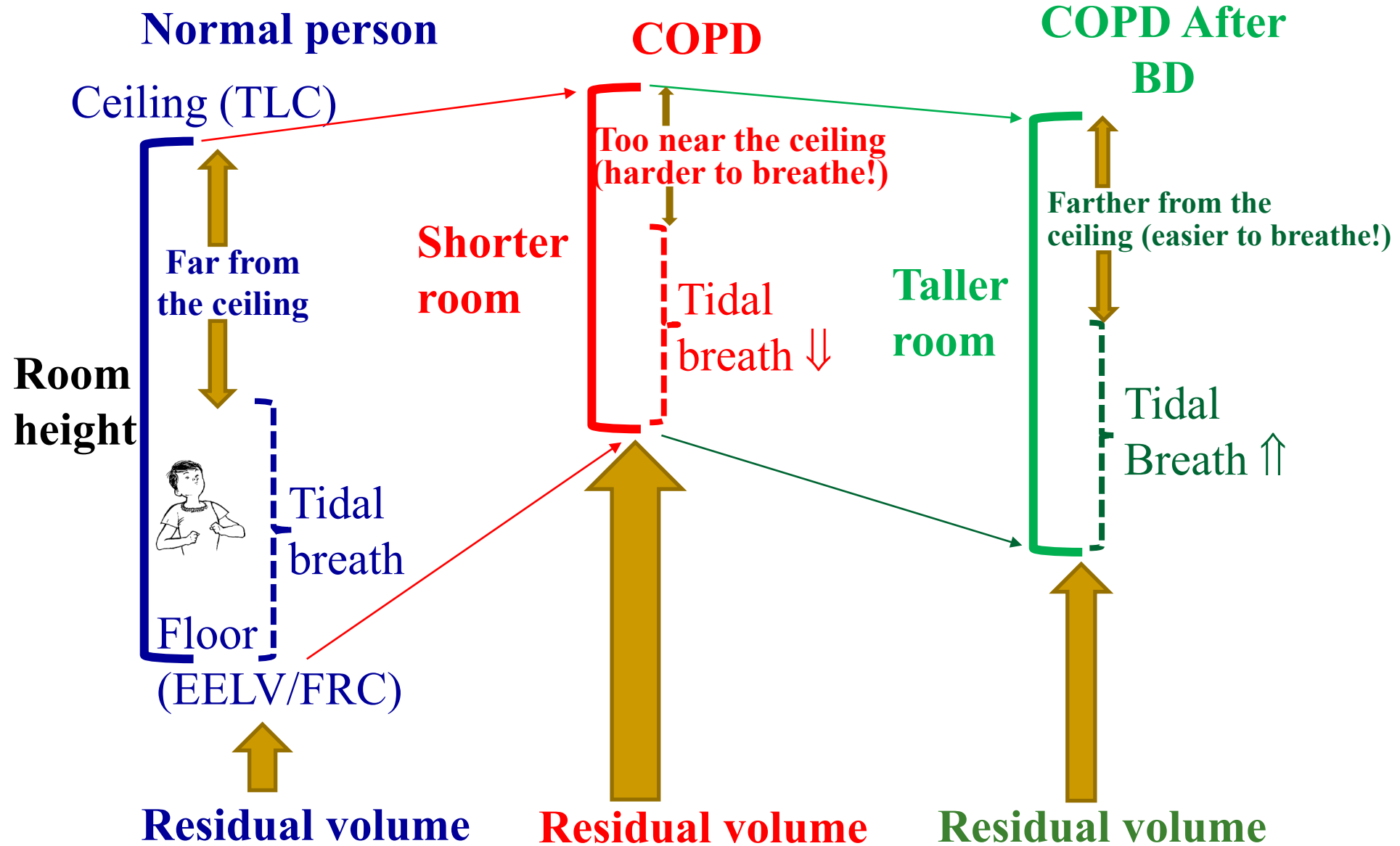
Shared risk factors

COPD

CV risk/disease

Shared risk factors
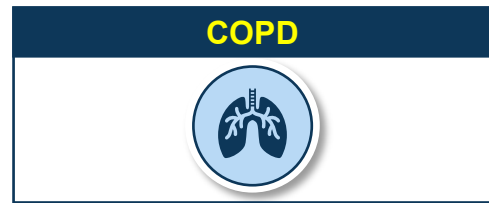
COPD

CV risk/disease

Exacerbations

Mechanical

Gas exchange

Systemic

Shared risk factors

COPD

Exacerbations

Mechanical
- ⇑ Expiratory flow limitation
- ⇑ Gas trapping/hyperinflation
- ⇑ Pleural swings

CV risk/disease

- ⇓ RV preload
- ⇑ RV afterload/PH
- ⇓ LV preload
- ⇑ LV afterload

Shared risk factors
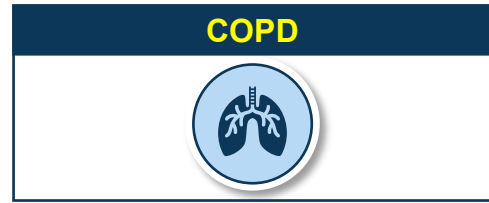
COPD

Exacerbations

Mechanical
- ⇑ Expiratory flow limitation
- ⇑ Gas trapping/hyperinflation
- ⇑ Pleural swings

Gas exchange
- ⇓ PaO_2
- ⇑ $PaCO_2$/ ⇓ pH

CV risk/disease

- ⇓ RV preload
- ⇑ RV afterload/PH
- ⇓ LV preload
- ⇑ LV afterload
- ⇓ Myocardial O_2 offer/demand
- ⇓ Cerebral vasoregulation

Shared risk factors
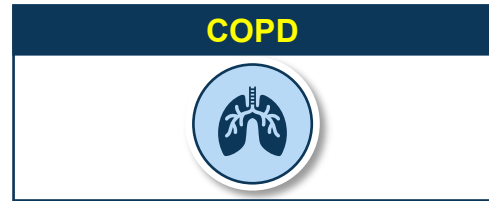
COPD

Exacerbations

Mechanical
- $\Uparrow$ Expiratory flow limitation
- $\Uparrow$ Gas trapping/hyperinflation
- $\Uparrow$ Pleural swings

Gas exchange
- $\Downarrow$ PaO_2
- $\Uparrow$ $PaCO_2$/ $\Downarrow$ pH

Systemic
- $\Uparrow$ Sympathetic outflow
- $\Uparrow$ Pro-inflammatory cytokines
- $\Uparrow$ Pro-thrombotic status

CV risk/disease

- $\Downarrow$ RV preload
- $\Uparrow$ RV afterload/PH
- $\Downarrow$ LV preload
- $\Uparrow$ LV afterload
- $\Downarrow$ Myocardial O_2 offer/demand
- $\Downarrow$ Cerebral vasoregulation
- $\Uparrow$ Peripheral vascular resistance
- $\Uparrow$ Thrombotic events
- $\Uparrow$ Plaque rupture

CV events and death
(MI, stroke, and acute HF)

Why do COPD patients with frequent exacerbations die earlier?

- **Because they are at particularly high risk of a potentially lethal cardiocirculatory event**

- **Because they are at more symptomatic, poorer functional status (including worse gas trapping/low D_{LCO}) to face the extra demands imposed by the exacerbation**

- **The joint effects of multiple co-morbidities, including lung cancer heart failure, anxiety-depression**

How can we improve our ability to detect exacerbations?
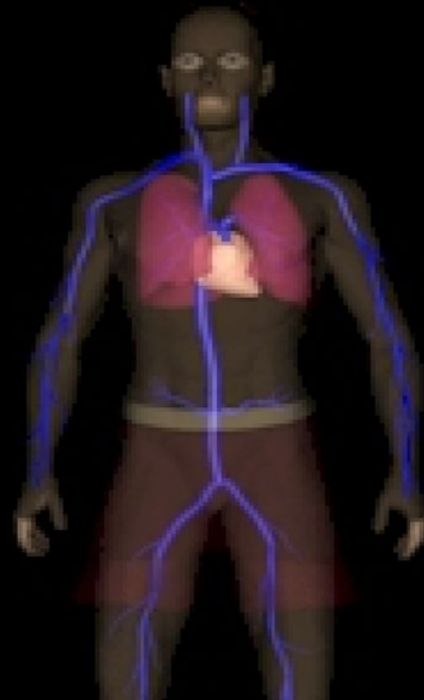
The majority of patients have exacerbations, and these are frequently unreported

Up to **77%** of patients with **COPD** have **at least 1 moderate or severe exacerbation** within a 3-year period…[1,a]
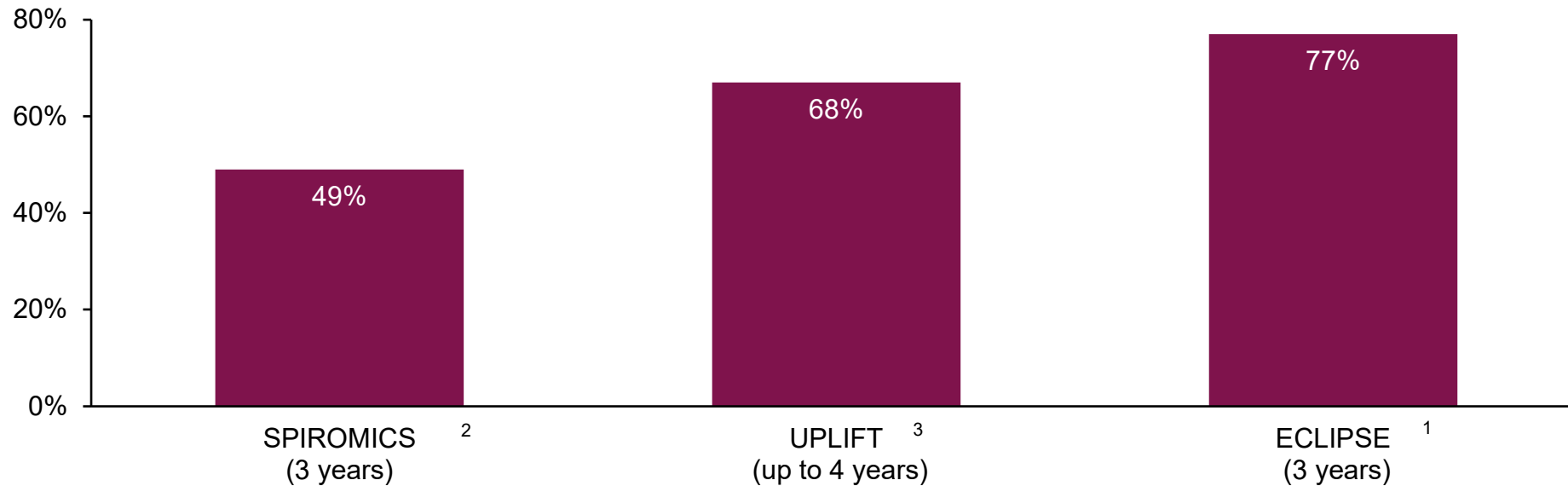
40–78% of COPD exacerbations are **not even reported**[4-7,b]

Reported exacerbations: the tip of the iceberg?

- **The "bad and good days" effect**

- **Confounded with worsening co-morbidity**

- **Extreme inactivity**

- **Denial (particularly in current smokers)**

- **Barriers to accessing medical care**

History of exacerbations and delayed maintenance therapy leads to and increased risk of subsequent exacerbations

Patients at **greatest risk** of future exacerbations are those who have a previous **history of exacerbations**[1,2,a]

Moderate or severe exacerbation
frequency in 12 months prior to observation: ☐ None ■ 1 or more

Moderate-to-severe exacerbation frequency during
12 months of follow up
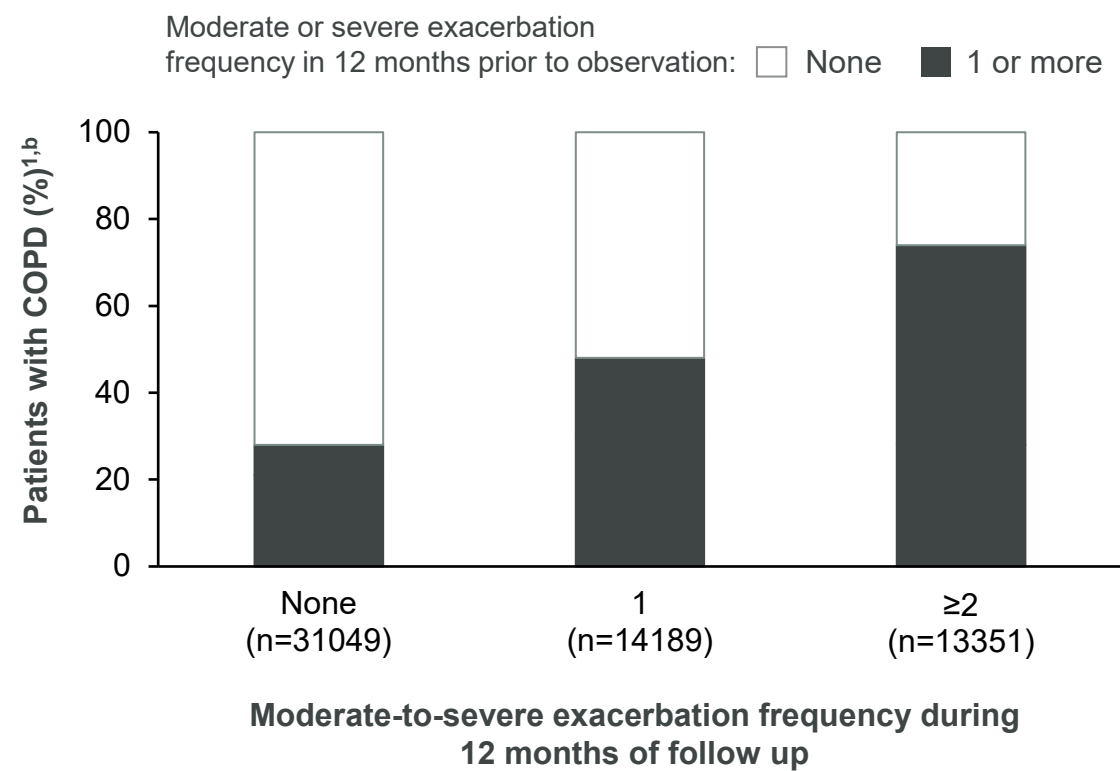
History of exacerbations and delayed maintenance therapy leads to and increased risk of subsequent exacerbations

Patients at **greatest risk** of future exacerbations are those who have a previous **history of exacerbations**[1,2,a]

Delaying maintenance therapy after a severe exacerbation is associated with an **increased risk** of future events[3,a]

Moderate or severe exacerbation frequency in 12 months prior to observation: ☐ None ■ 1 or more

Patients with COPD (%)[1,b]

None
(n=31049)

1
(n=14189)

≥2
(n=13351)

Moderate-to-severe exacerbation frequency during 12 months of follow up
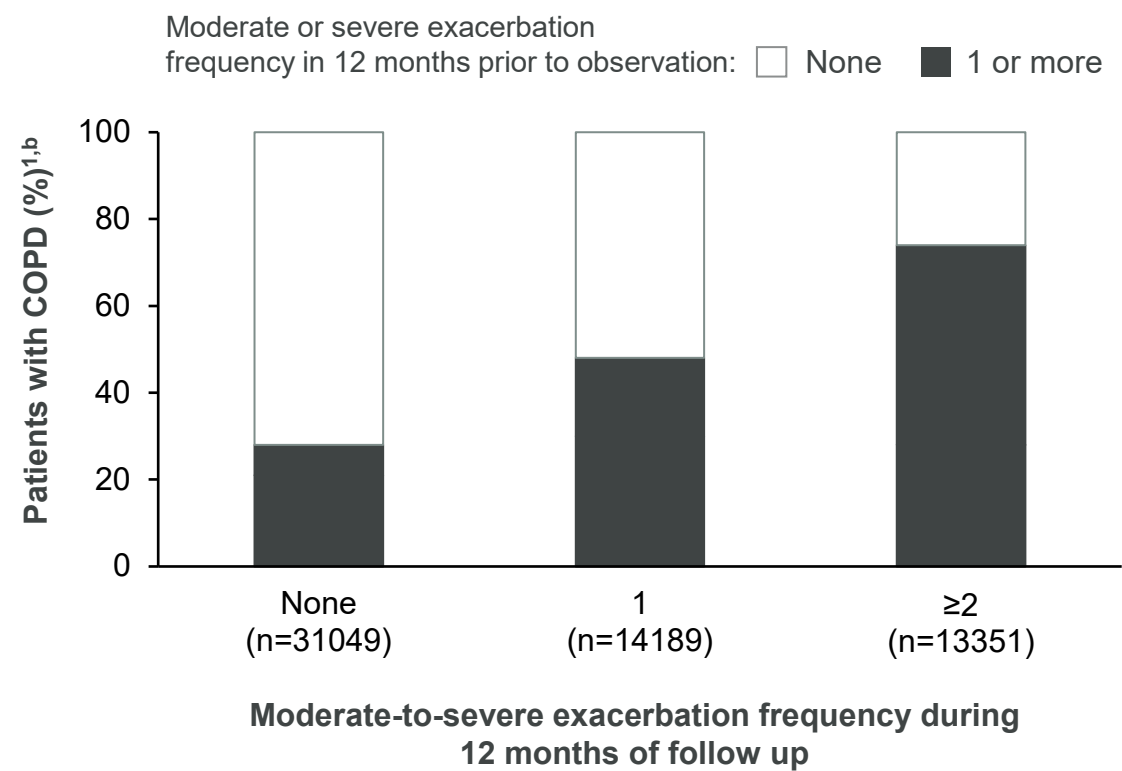
68% increased risk of a moderate/severe exacerbation

79% increased risk of a severe exacerbation

Identifying patients at risk of exacerbations is key to optimizing their management
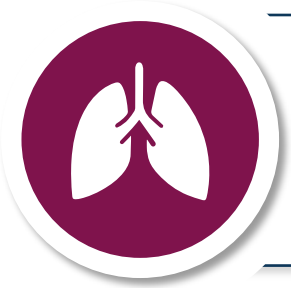
A history of COPD exacerbations is a strong predictor of future exacerbations[1,2]

Increased breathlessness is associated with higher exacerbation risk[1]

Patients with raised eosinophil counts <u>not</u> on ICS are at higher risk of exacerbating[3]

30 1. Müllerová H et al. *BMJ Open*. 2014;4:e006171; 2. Hurst JR et al. *N Engl J Med*. 2010;363:1128–1138; 3. Bafadhel M et al. *Lancet Respir Med*. 2018;6:117–126.

How can we improve our ability to detect the frequent exacerbator?

• **Track more carefully the exacerbation history, looking for unreported events**

• **Measure eosinophils (if not on ICS)**

• **Measure dyspnea burden systematically**

DEVELOP A WAY TO FLAG OUT THE FREQUENT EXACERBATOR, REASSESSING THE <u>VERY HIGH RISK</u> AS FREQUENTLY AS POSSIBLE PARTICULARLY ≥2 EXAC/YR, MRC ≥3, EOSINO ≥200-300

What are the adjunct (to foundation treatment) measures to reduce exacerbation burden?

Each exacerbation accelerates the rate of subsequent exacerbations resulting in a significant impact on a patient's quality of life

After the first severe exacerbation, the **time between subsequent exacerbations shortens**[1,a]

Median time (years) to subsequent exacerbation[3]

5.4   1.6   0.9   0.7   0.5   0.4

1   2   3   4   5   6   7

Exacerbation sequence number
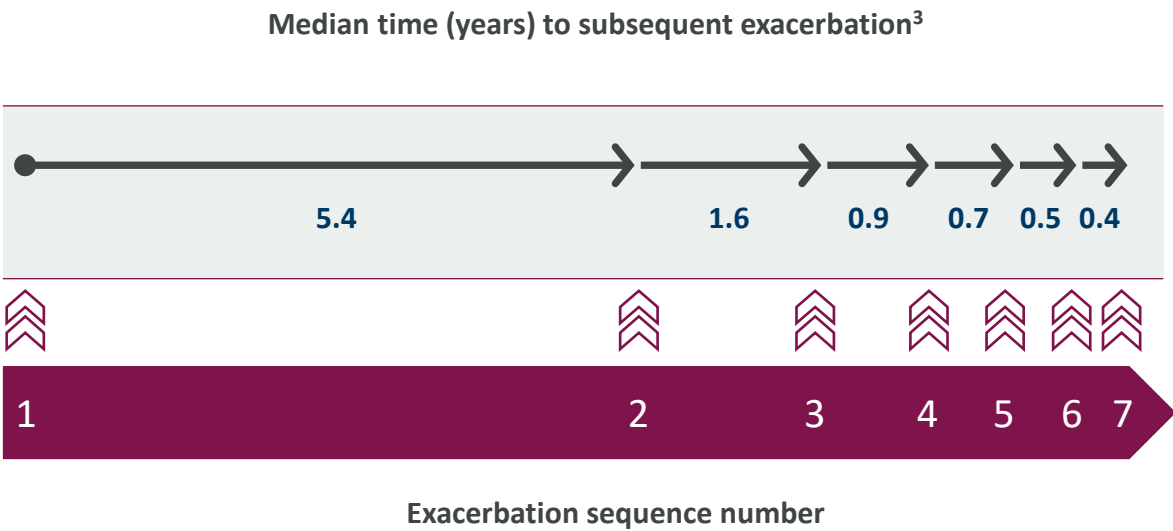
aAdjusted for age, sex, calendar time (cohort entry prior to 2000), and the modified Chronic Disease Score divided in quartiles with a fifth category to account for patients with no or partial medication information in the year prior to cohort entry

1. Suissa S et al. *Thorax*. 2012;67:957–963 2. Hurst JR et al. *Eur J Int Med*. 2020;73:1.

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Median time (years) to subsequent exacerbation[3]

5.4   1.6   0.9   0.7   0.5   0.4

1   2   3   4   5   6   7

Exacerbation sequence number

…and these have a **significant impact on patients**[8]
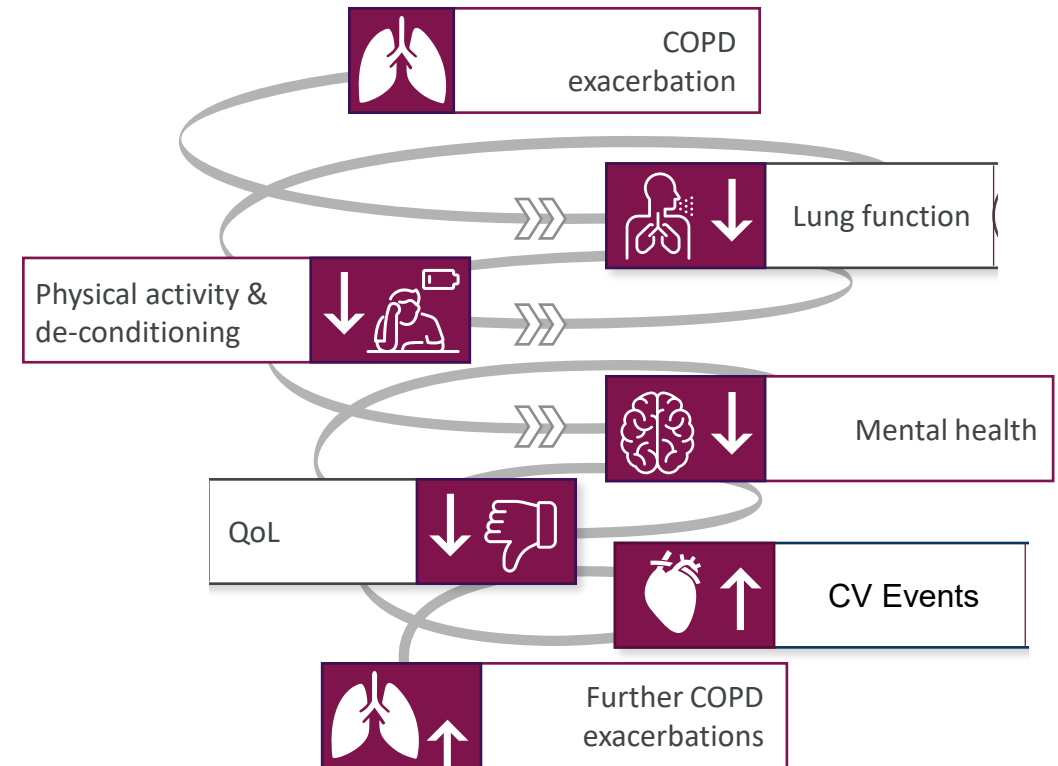
COPD exacerbation

Lung function

Physical activity & de-conditioning

Mental health

QoL

CV Events

Further COPD exacerbations

aAdjusted for age, sex, calendar time (cohort entry prior to 2000), and the modified Chronic Disease Score divided in quartiles with a fifth category to account for patients with no or partial medication information in the year prior to cohort entry

1. Suissa S et al. *Thorax*. 2012;67:957–963 2. Hurst JR et al. *Eur J Int Med*. 2020;73:1.

Antibiotics (macrolides)

Azithromycin (250 mg/day or 500 mg three times per week) or erythromycin (500 mg two times per day) for one year reduces the risk of exacerbations in patients prone to exacerbations.[160-162] Azithromycin use showed a reduced exacerbation rate in former

Study or Subgroup	Antibiotics Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 Continuous antibiotics						
Albert 2011	317	558	380	559	40.2%	0.62 [0.49, 0.79]
He 2010	9	18	14	18	5.2%	0.29 [0.07, 1.21]
Seemungal 2008	28	53	42	56	13.5%	0.37 [0.17, 0.84]
Subtotal (95% CI)		629		633	58.9%	**0.55 [0.39, 0.77]**
Total events	354		436			

Heterogeneity: Tau² = 0.02; Chi² = 2.34, df = 2 (P = 0.31); I² = 14%
Test for overall effect: Z = 3.41 (P = 0.0006)

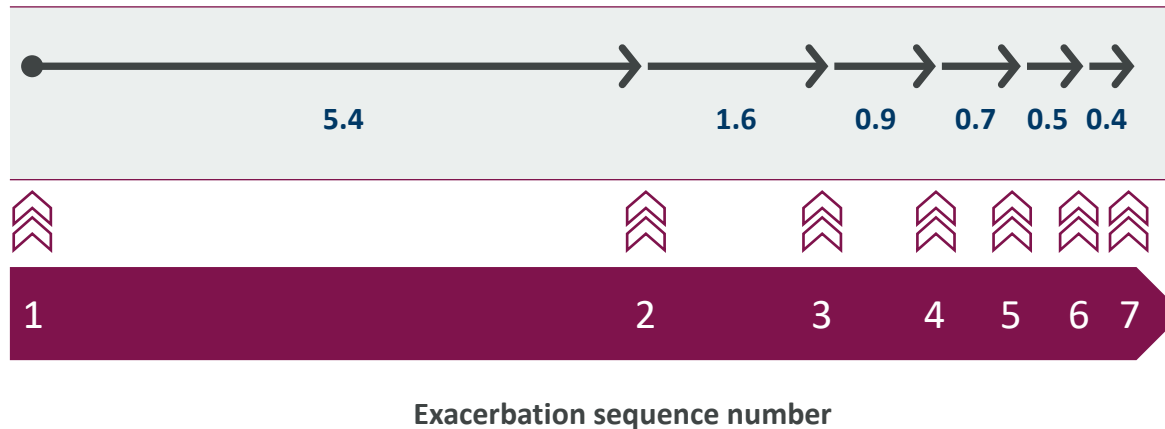| Study or Subgroup	Antibiotics Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.2 Pulsed antibiotics						
Sethi 2010	269	569	295	580	41.1%	0.87 [0.69, 1.09]
Subtotal (95% CI)		569		580	41.1%	**0.87 [0.69, 1.09]**
Total events	269		295			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.22 (P = 0.22)

Total (95% CI)		1198		1213	100.0%	**0.64 [0.45, 0.90]**
Total events	623		731			

Heterogeneity: Tau² = 0.06; Chi² = 7.97, df = 3 (P = 0.05); I² = 62%
Test for overall effect: Z = 2.53 (P = 0.01)
Test for subgroup differences: Chi² = 4.66, df = 1 (P = 0.03), I² = 78.6%

Favours antibiotic   Favours placebo

Long-term azithromycin and erythromycin therapy reduces exacerbations over one year (**Evidence A**).

Treatment with azithromycin is associated with an increased incidence of bacterial resistance (**Evidence A**) and hearing test impairment (**Evidence B**).

Herath 2013, Cochrane Database Syst Rev

PDE4 inhibitor (roflumilast)

Roflumilast vs placebo
Outcome: COPD exacerbations

Fig. 9 Effect of roflumilast vs. placebo on incidence of COPD exacerbation (number per patient per year). CI, confidence interval; COPD, chronic obstructive pulmonary disease; SD, standard derivation
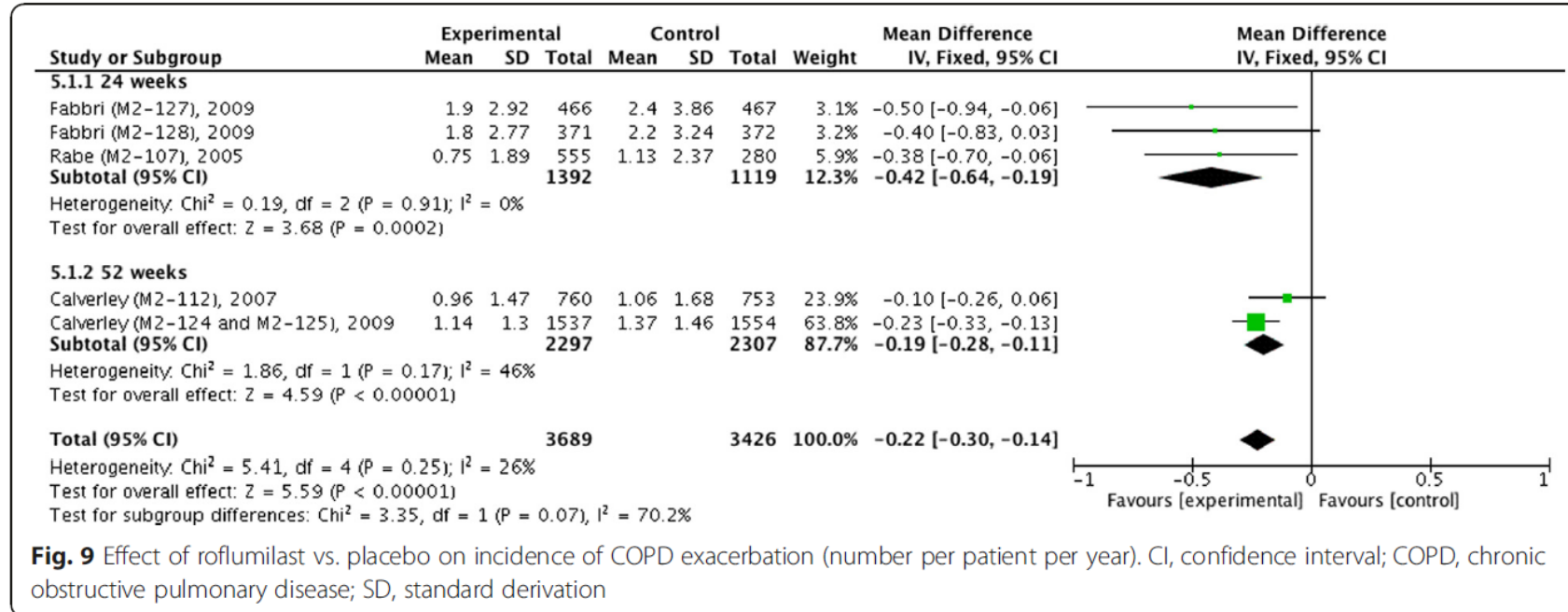
In patients with chronic bronchitis, severe to very severe COPD and a history of exacerbations:

o A PDE4 inhibitor improves lung function and reduces moderate and severe exacerbations (**Evidence A**).

Luo 2016, Respir Res

| Introduction | Physician | Patient | Population | General |

Mucolytic *vs* placebo
Outcome: COPD exacerbations

Mucolytic agents
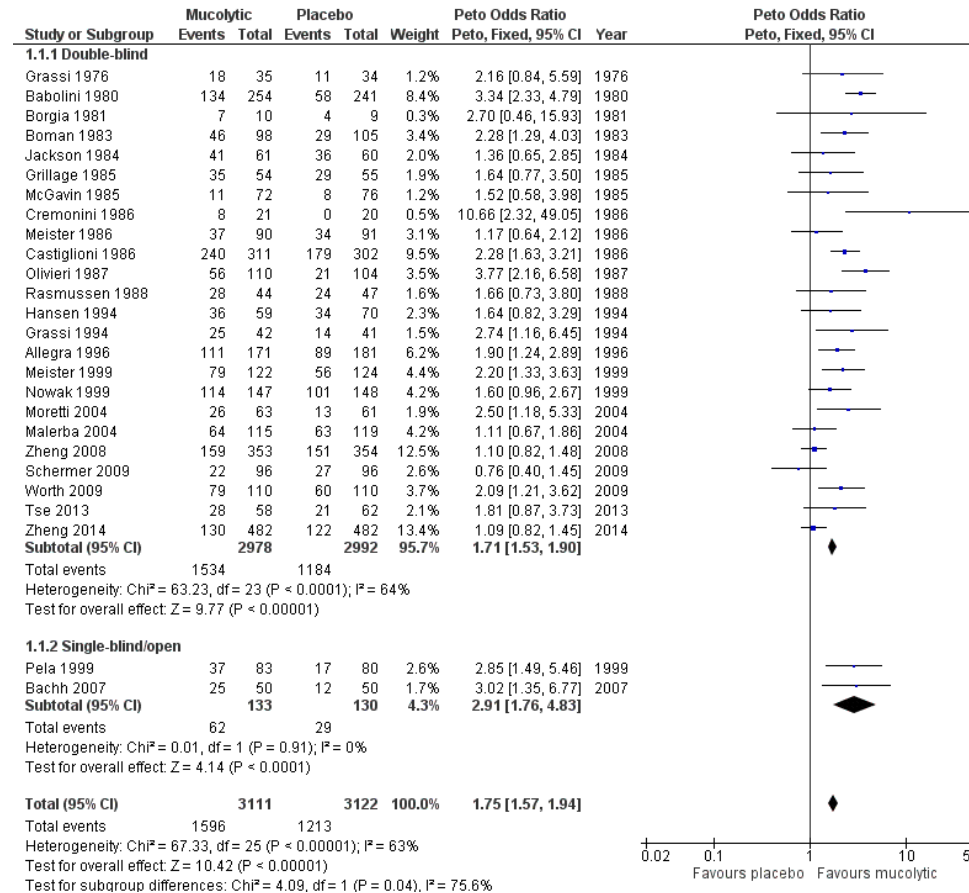
Regular use of NAC and carbocysteine reduces the risk of exacerbations in select populations (**Evidence B**).

Introduction	Physician	Patient	Population	General

Oscillatory Positive Expiratory Pressure Devices

Acapella

**Alone or post-nebulization with
isotonic saline (eventually hypertonic)**

AECOPD Prevention Checklist

- ☑ **Smoking cessation**

- ☑ **Vaccinations**

- ☑ **Self-management education (inhaler instruction) with Case Manager and written Action Plan (antibiotic/<u>low </u>dose OCS)**

- ☑ **Regular triple therapy (LAMA + ICS/LABA)**

- ☑ **Activity promotion / pulmonary rehab**

- ☑ **Consider PDE4 inhibitors, macrolide prophylaxis and NAC . TREAT POST-NASAL DRIP AND GERD!**

Can triple therapy reduce all-cause mortality?
If so, how?
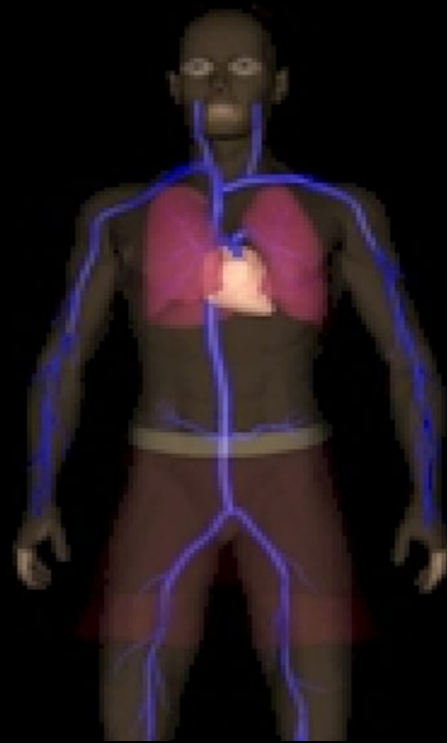
COPD Treatment- The Key Points

Dyspnea

Most patients with comorbid HF (regardless of exacerbation history) ⇓

	MILD ("less")	**MOD/SEVERE ("more")**
YES	**LABA / ICS (+ LAMA?)**	**LAMA + LABA/ICS**
NO	**LAMA OR LABA**	**LAMA + LABA**

Exacerbator

The current global treatment paradigm for managing exacerbations is one of stepwise treatment escalation

A **stepwise treatment** approach **may allow for disease progression** and long-term damage[1,2]

Bronchodilator → LAMA or LABA → LAMA/LABA or ICS/LABA → ICS/LAMA/LABA

Accelerated lung function decline after each exacerbation

A single moderate or severe exacerbation may almost double the rate of lung function decline[1]

ICS/LAMA/LABA is used late in disease progression, following multiple exacerbations[3]

⭐ Exacerbation[a]

Time
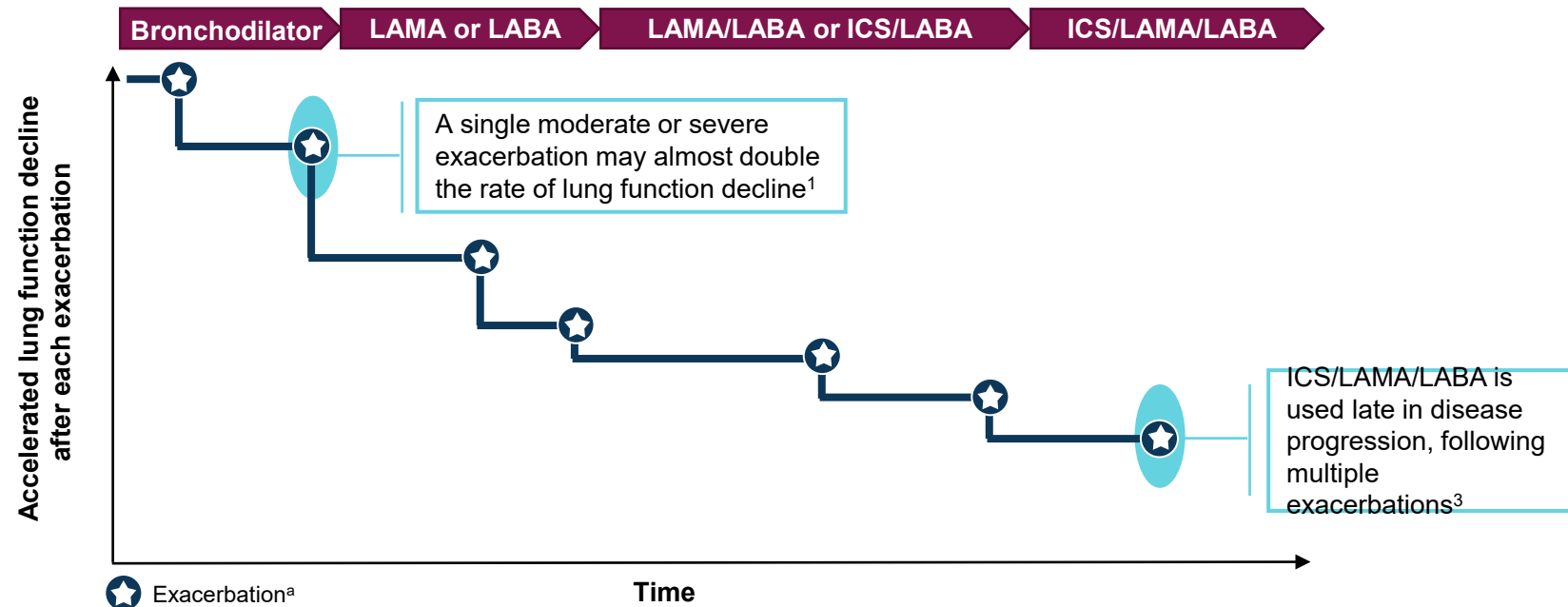
[a]Graph is an illustration of a typical journey for a patient with COPD experiencing exacerbations

1. Dransfield MT et al. *Am J Respir Crit Care Med*. 2017;195:324-330; 2. Watz H et al. *Respir Res*. 2018;19:251; 3. GOLD. Global strategy for the diagnosis, management, and prevention of COPD: 2020 report.

The information provided here is for scientific exchange purposes only. AstraZeneca does not, under any circumstances, promote its products for off-label or unapproved uses

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Study Design: ETHOS STUDY

Phase III, randomized, double-blind, parallel-group, 52-week trial conducted in 26 countries[1,2]

All treatments were administered twice daily via a single AEROSPHERE™ inhaler

SCREENING

All patients were on open-label ipratroprium QID ± ICS[a]

RANDOMIZATION[b]

BUD/GLY/FORM MDI 320/14.4/10 µg BID (ICS/LAMA/LABA)	(n=2157)
BUD/GLY/FORM MDI 160/14.4/10 µg BID (ICS/LAMA/LABA)	(n=2137)
GLY/FORM MDI 14.4/10 µg BID (LAMA/LABA)	(n=2143)
BUD/FORM MDI[c] 320/10 µg BID (ICS/LABA)	(n=2151)

Double-blind treatment period[a] ——— **Follow-up**

Visit	1	2	3	4	5	6[d]	7	8[d]	9[d]	10	11[d]	12	13[d]	14	☎
Week	−4			0	4	8	12	16	20	24	28	36	44	52	54

Assess bronchodilator response[e]

[a]All patients received albuterol sulfate for rescue use as needed; [b]Randomization was stratified by exacerbation history (1 or ≥2 moderate/severe exacerbations), postbronchodilator FEV_1 (25% to <50% or 50% to <65% predicted), blood eosinophil count (<150 or ≥150 cells/mm^3), and country; [c]BUD/FORM MDI delivered via the AEROSPHERE™ inhaler is not an available product; [d]Visit conducted via telephone contact; all other visits were conducted in the clinic; [e]Reversibility to a SABA (for classification) was tested at Visit 2 and to a SAMA (for characterization) was tested at Visit 3.

44   1. Rabe KF et al. *Respir Med*. 2019;158:59-66; 2. Rabe KF et al. Article and supplementary appendix. *N Engl J Med*. 2020;383:35-48.

Study Population

Patient Population

Moderate to very severe COPD with a **history of moderate or severe exacerbation(s)**

Key Inclusion Criteria

40-80 years of age
Current or former smoker (≥10 pack-year history)
Symptomatic (CAT ≥10)
On ≥2 inhaled maintenance therapies[a] for COPD for ≥6 weeks prior to screening

Postbronchodilator FEV_1 25-65% of predicted normal

History of moderate or severe COPD exacerbations in the 12 months prior to screening:
- **≥1 moderate/severe if FEV_1 <50% of predicted normal or**
- **≥2 moderate or ≥1 severe if FEV_1 ≥50% of predicted normal**

Key Exclusion Criteria

Current diagnosis of asthma
COPD due to α_1-antitrypsin deficiency
Significant diseases or conditions other than COPD
Acute worsening of COPD ≤6 weeks prior to screening, resulting in treatment with OCS or antibiotics

BUD 320/GLY/FORM Significantly Reduced Risk of All-Cause Mortality vs. LAMA/LABA[a]
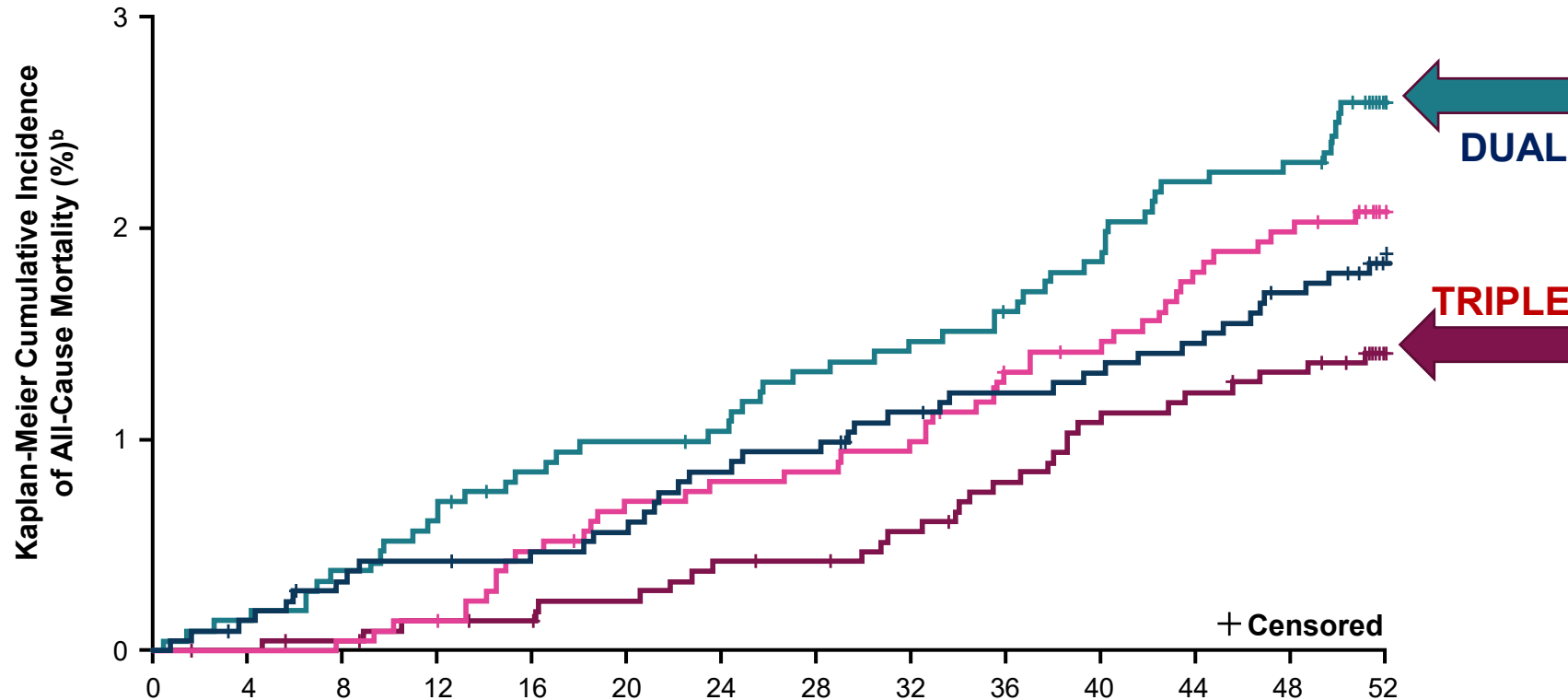
Patients at Risk													
BUD/GLY/FORM 320/14.4/10 µg	2137	2136	2134	2131	2130	2127	2123	2122	2118	2112	2106	2103	2100	2075
BUD/GLY/FORM 160/14.4/10 µg	2121	2121	2120	2118	2110	2104	2102	2101	2098	2087	2084	2076	2072	2062
GLY/FORM 14.4/10 µg	2120	2117	2112	2106	2100	2097	2095	2089	2086	2082	2077	2069	2067	2045
BUD/FORM 320/10 µg	2131	2127	2122	2120	2118	2116	2110	2108	2102	2099	2097	2094	2088	2075

Adapted from Martinez FJ et al. Article and supplement in press. *Am J Crit Care Med*. 2020.

BUD 320/GLY/FORM Significantly Reduced Risk of All-Cause Mortality vs. LAMA/LABA[a]

Over 52 weeks
BUD/GLY/FORM 320/14.4/10 µg
demonstrated a:

49%

**significant reduction
vs. LAMA/LABA[c]**

HR: 0.51; 95% CI: 0.33 to 0.80;
unadjusted p=0.0035[a]

NNT = 80 vs. LAMA/LABA
(95% CI: 58 to 198)

28% reduction vs. ICS/LABA
HR: 0.72; 95% CI: 0.44 to 1.16; p=0.1721

DUAL

TRIPLE

+ Censored

Kaplan-Meier Cumulative Incidence
of All-Cause Mortality (%)[b]

Weeks

Patients at Risk	0	4	8	12	16	20	24	28	32	36	40	44	48	52
BUD/GLY/FORM 320/14.4/10 µg	2137	2136	2134	2131	2130	2127	2123	2122	2118	2112	2106	2103	2100	2075
BUD/GLY/FORM 160/14.4/10 µg	2121	2121	2120	2118	2110	2104	2102	2101	2098	2087	2084	2076	2072	2062
GLY/FORM 14.4/10 µg	2120	2117	2112	2106	2100	2097	2095	2089	2086	2082	2077	2069	2067	2045
BUD/FORM 320/10 µg	2131	2127	2122	2120	2118	2116	2110	2108	2102	2099	2097	2094	2088	2075

Adapted from Martinez FJ et al. Article and supplement in press. *Am J Crit Care Med*. 2020.

BUD 320/GLY/FORM Consistently Reduced Time to Death vs. LAMA/LABA in All Datasets

BUD 320/GLY/FORM (n=2137) vs. **GLY/FORM (n=2120)**

BUD 320/GLY/FORM (n=2137) vs. **BUD/FORM (n=2131)**

Patients With an Event, n (%)

On- and Off-treatment (original dataset)
49 (2.3)   28 (1.3)   34 (1.6)

0.54 (0.34 to 0.87) p=0.0111[a]

0.78 (0.47 to 1.30) p=0.3401

On- and Off-treatment (final retrieved dataset)
56 (2.6)   30 (1.4)   40 (1.9)

0.51 (0.33 to 0.80) p=0.0035[a]

0.72 (0.44 to 1.16) p=0.1721

On-treatment[b] (final retrieved dataset)
45 (2.1)   25 (1.2)   28 (1.3)

0.50 (0.30 to 0.81) p=0.0056[a]

0.82 (0.47 to 1.41) p=0.4640

0.25   0.5   1   2

Favors Triple

HR (95% CI)

0.25   0.5   1   2

Favors Triple

HR (95% CI)

As in the original dataset, the risk of death on- and off-treatment in the final retrieved dataset was significantly lower with BUD 320/GLY/FORM vs. LAMA/LABA (unadjusted p=0.0035[a]), equivalent to a **NNT of 80** (95% CI: 58 to 198)

BUD 320/GLY/FORM Mortality Benefit Seen Across Many Subgroups and Analyses

Landmark Timepoint Analyses

Additional analyses illustrate that the mortality results do not appear to be driven by early ICS withdrawal

Numerical benefits for the time to death favoring BUD 320/GLY/FORM vs. dual therapies were shown across subgroups of:

Prior exacerbation history *(moderate/severe and severe)*

Baseline postbronchodilator FEV$_1$ % predicted

Prior triple therapy use

Patients on ICS at screening

Incidence of Death by Blood Eosinophil Count
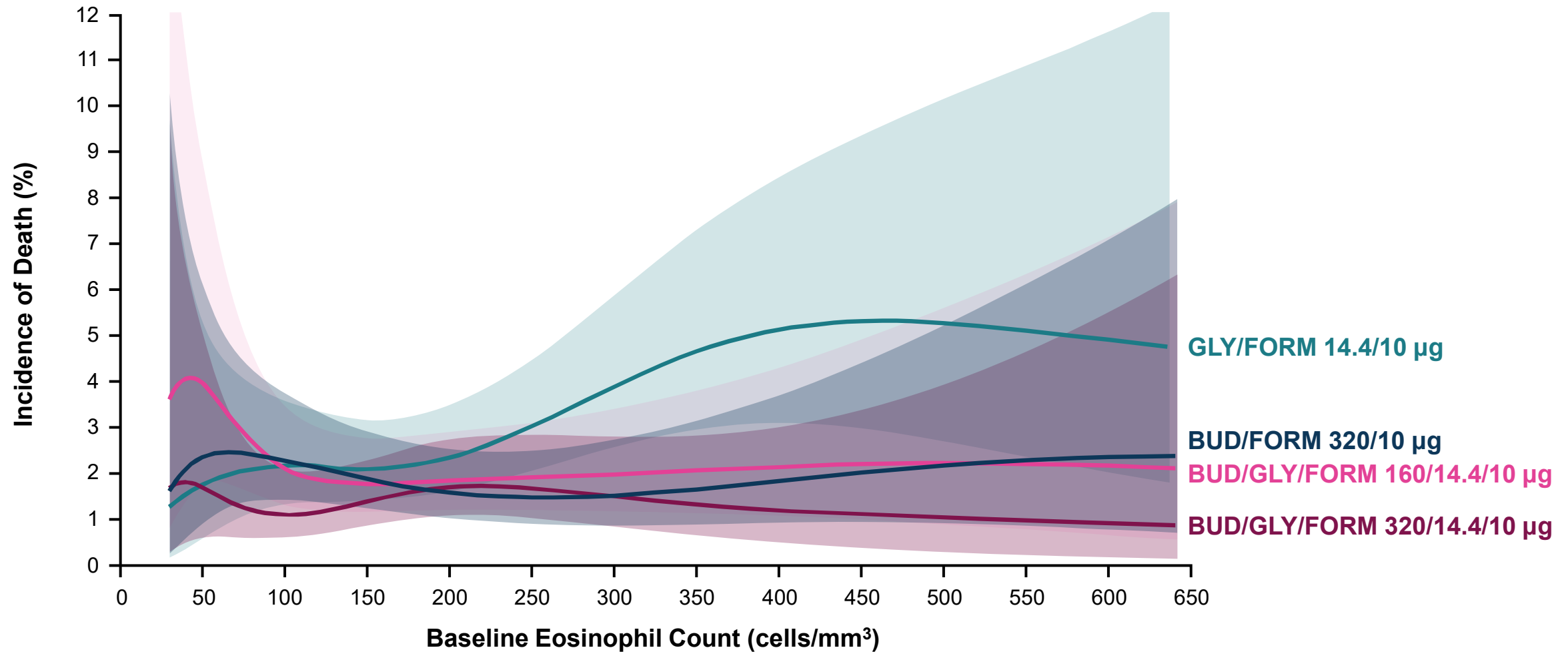
Notes: ITT population. All treatments were administered BID. Data from generalized additive model. Banded areas indicate 95% CI that reflect the skewed distribution of eosinophil counts, i.e., 17.3% of patients had counts <100 cells/mm³, 67.9% had 100–300 cells/mm³, and 14.7% had >300 cells/mm³.

Adapted from Martinez FJ et al. Article and supplement in press. *Am J Crit Care Med*. 2020.

Cardiovascular causes were the most common adjudicated cause of death in ETHOS

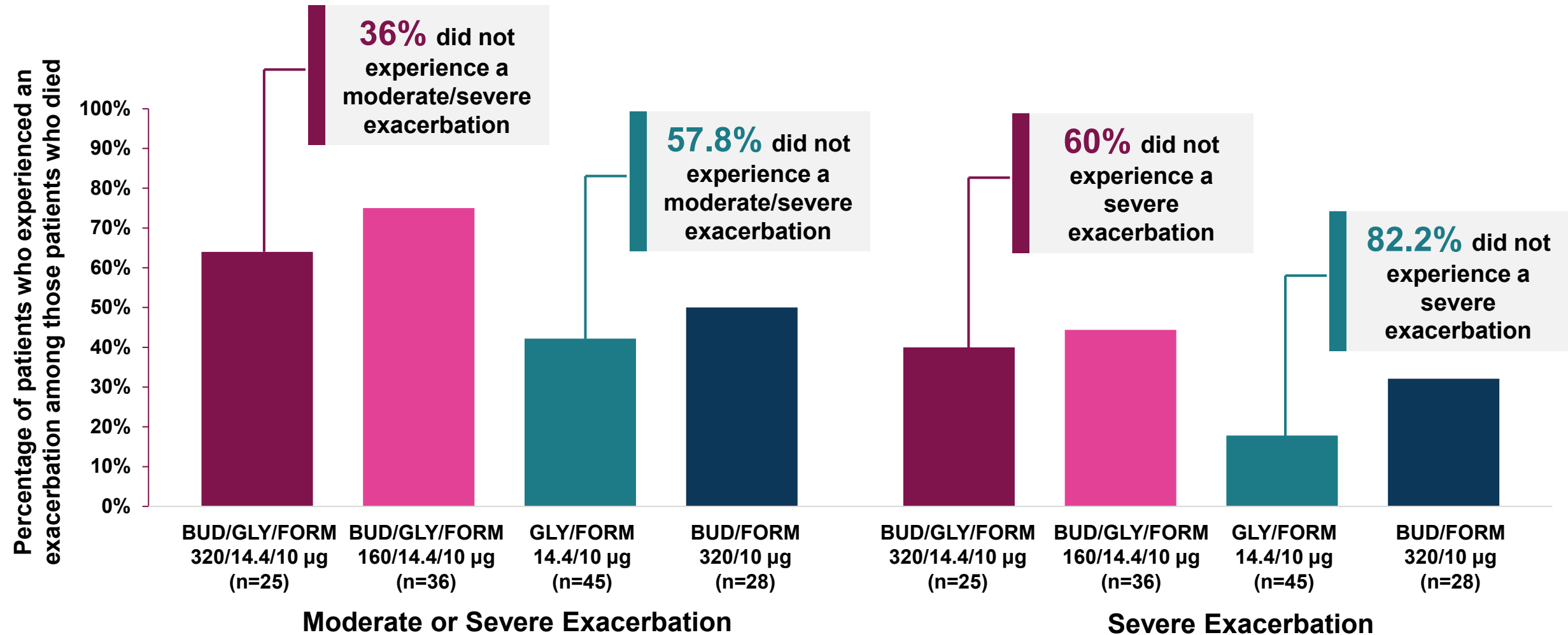| Summary of On- and Off-Treatment Deaths	BUD/GLY/FORM 320/14.4/10 µg (n=2137)	BUD/GLY/FORM 160/14.4/10 µg (n=2121)	GLY/FORM 14.4/10 µg (n=2120)	BUD/FORM 320/10 µg (n=2131)
Total Number of Deaths,[a] n (%)				
Original dataset	30 (1.4)	44 (2.1)	52 (2.5)	38 (1.8)
Final retrieved dataset	37 (1.7)	55 (2.6)	64 (3.0)	46 (2.2)
Deaths Included in the Time to Death Analysis,[b] n (%)				
Original dataset	28 (1.3)	39 (1.8)	49 (2.3)	34 (1.6)
Final retrieved dataset	30 (1.4)	44 (2.1)	56 (2.6)	40 (1.9)
Adjudicated Deaths,[c] n (%)				
Original dataset	27 (1.3)	42 (2.0)	47 (2.2)	35 (1.6)
Final retrieved dataset[d]	28 (1.3)	43 (2.0)	50 (2.4)	35 (1.6)
Cardiovascular	11 (0.5)	16 (0.8)	29 (1.4)	11 (0.5)
Respiratory	7 (0.3)	13 (0.6)	8 (0.4)	6 (0.3)
COPD	5 (0.2)	7 (0.3)	5 (0.2)	5 (0.2)
Pneumonia	2 (<0.1)	3 (0.1)	3 (0.1)	1 (<0.1)
Other respiratory	0	3 (0.1)	0	0
Cancer	2 (<0.1)	6 (0.3)	3 (0.1)	7 (0.3)
Other	8 (0.4)	8 (0.4)	10 (0.5)	11 (0.5)
Nonadjudicated Deaths (all-cause), n (%)				
Original dataset	3 (0.1)	2 (<0.1)	5 (0.2)	3 (0.1)
Final retrieved dataset	9 (0.4)	12 (0.6)	14 (0.7)	11 (0.5)

Notes: ITT population. All treatments were administered BID.

[a]Includes all reported deaths occurring at any time after the first dose of treatment, without restriction as to how late the death was observed; [b]Includes deaths up to and including the Week 52 visit; [c]Only deaths that were associated with ≥1 SAE were adjudicated (ie, vital status of death without a known associated AE was not adjudicated); [d]The 5 additional causes of death adjudicated in the final retrieved dataset were as follows: Cardiovascular, n=1 (in the GLY/FORM group); Other, n=4 (2 in the GLY/FORM group and 1 each in the BUD 320/GLY/FORM and BUD 160/GLY/FORM groups).

Martinez FJ et al. Article and supplement in press. *Am J Crit Care Med*. 2020. © AstraZeneca 2020

Among Patients Who Died On-Treatment, Many Had Not Experienced an Exacerbation

36% did not experience a moderate/severe exacerbation

57.8% did not experience a moderate/severe exacerbation

60% did not experience a severe exacerbation

82.2% did not experience a severe exacerbation

Percentage of patients who experienced an exacerbation among those patients who died

Moderate or Severe Exacerbation

- BUD/GLY/FORM 320/14.4/10 µg (n=25)
- BUD/GLY/FORM 160/14.4/10 µg (n=36)
- GLY/FORM 14.4/10 µg (n=45)
- BUD/FORM 320/10 µg (n=28)

Severe Exacerbation

- BUD/GLY/FORM 320/14.4/10 µg (n=25)
- BUD/GLY/FORM 160/14.4/10 µg (n=36)
- GLY/FORM 14.4/10 µg (n=45)
- BUD/FORM 320/10 µg (n=28)

Notes: mITT population. All treatments were administered BID. n = the number of patients who died in each treatment arm

Martinez FJ et al. Article and supplement in press. *Am J Crit Care Med*. 2020

Clinical Message

- **A LARGE FRACTION OF EXACERBATORS DIE <u>NOT DURING</u> EXACERBATIONS BUT <u>IN-BETWEEN</u> EXACERBATIONS OR EVEN IF THEY <u>DO NOT PRESENT WITH EXACERBATIONS DURING THE STUDY</u>**

- **LIKELY REFLECTING THE CUMULATIVE IMPACT OF THE RISK FACTORS, HIGH CARDIOVASCULAR RISK**

BUD 320/GLY/FORM Mortality Benefit Seen Across Many Subgroups and Analyses

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Additional analyses illustrate that the mortality results do not appear to be driven by early ICS withdrawal

Numerical benefits for the time to death favoring BUD 320/GLY/FORM vs. dual therapies were shown across subgroups of:

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(moderate/severe and severe)

Baseline postbronchodilator FEV_1 % predicted

Prior triple therapy use

Patients on ICS at screening

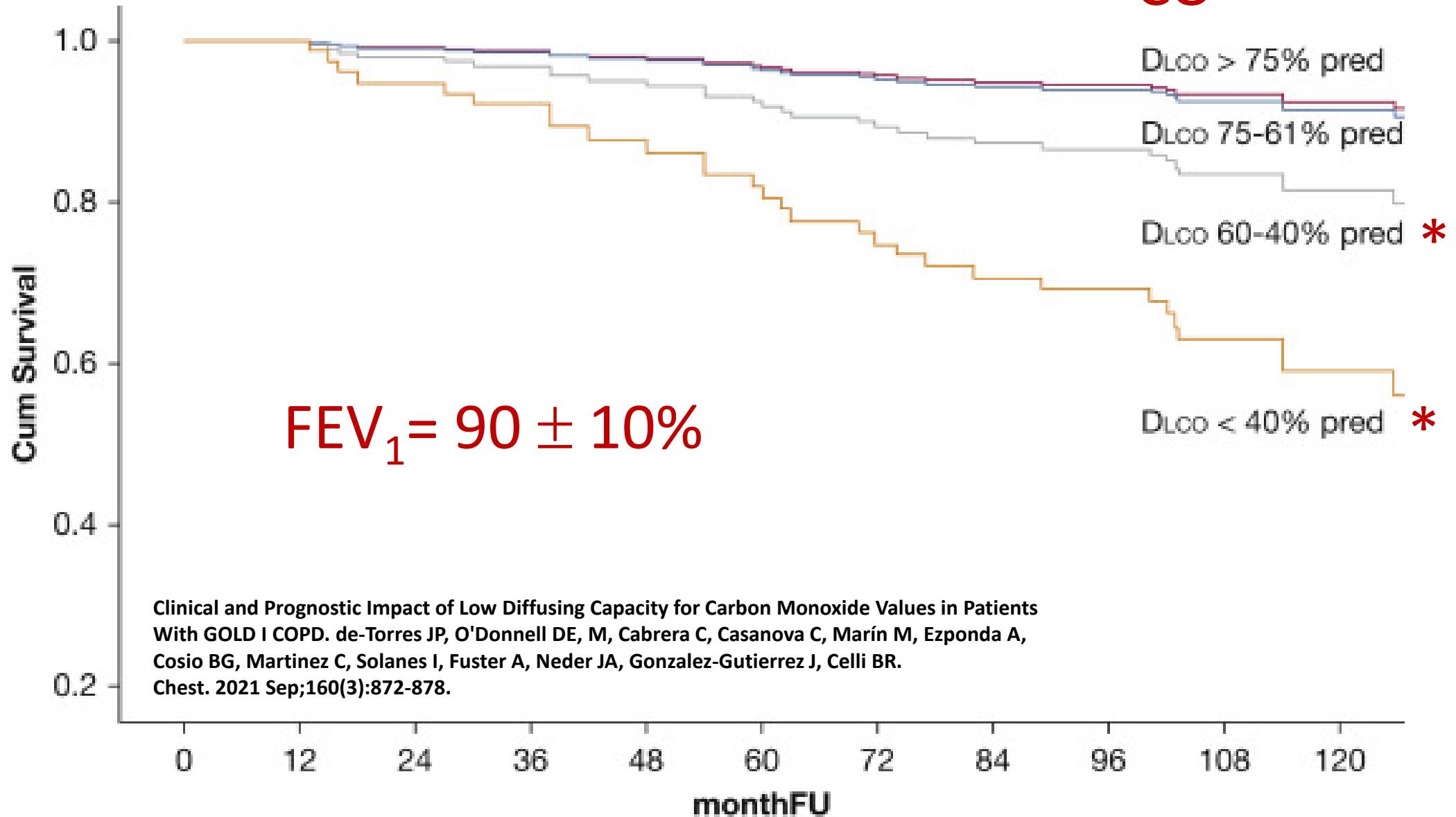The reduction in mortality seen for BUD 320/GLY/FORM cannot be explained solely by exacerbation reduction

The benefit of BUD 320/GLY/FORM vs. LAMA/LABA in reducing mortality generally increased with eosinophil count

Tipping point analyses illustrated that the mortality results were robust to missing data

Martinez FJ et al. Article and supplement in press. *Am J Crit Care Med*. 2020.

Never ignores a low $D_{L_{CO}}$!

FEV$_1$= 90 ± 10%

Clinical and Prognostic Impact of Low Diffusing Capacity for Carbon Monoxide Values in Patients With GOLD I COPD. de-Torres JP, O'Donnell DE, M, Cabrera C, Casanova C, Marín M, Ezponda A, Cosio BG, Martinez C, Solanes I, Fuster A, Neder JA, Gonzalez-Gutierrez J, Celli BR. Chest. 2021 Sep;160(3):872-878.

Potential mechanisms of ICS – containing therapy on mortality benefit in patients with associated CV disease

Hyperinflation

May **reduce hyperinflation** in combination with a bronchodilator, potentially improving cardiac function through improved respiratory mechanics and beneficial effects on cardiac structure, function, and pulmonary vasculature[1-3]

Exacerbation

Reduce exacerbation events, which may lead to reduced MACE, hospitalizations, cardiovascular diseases, and CV death[3-5,6,7]

Inflammation

May **reduce various markers of systemic inflammation**, potentially improving cardiac function[3,8]

May **reduce lung-specific mediators of inflammation**, resulting in improved lung function and health status in patients with COPD[9]

Avoid chronic and acute overloading of the dysfunctional cardiopulmonary unit!

IMPACT TRIAL: TRIPLE AND LABA/ICS WERE SUPERIOR TO LABA/LAMA IN REDUCING MORTALITY
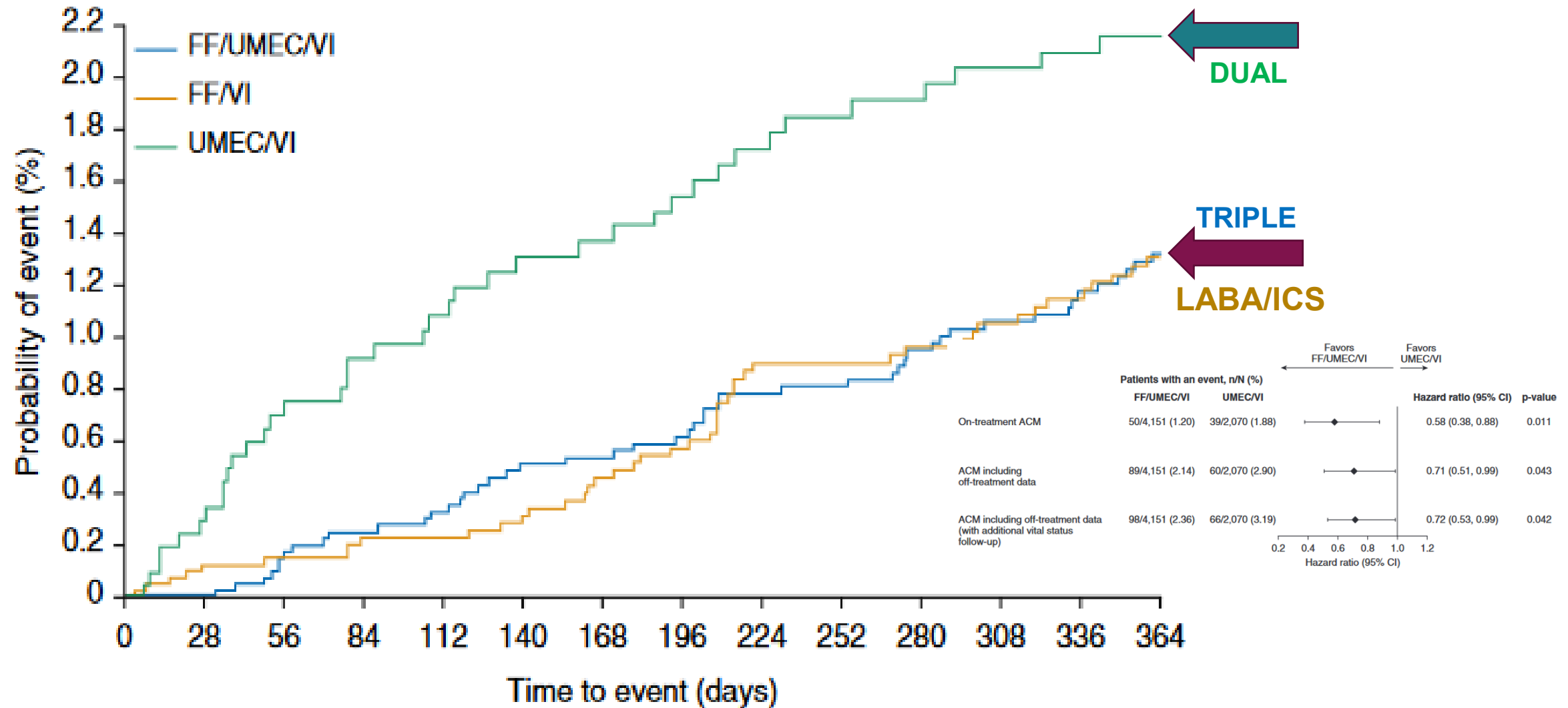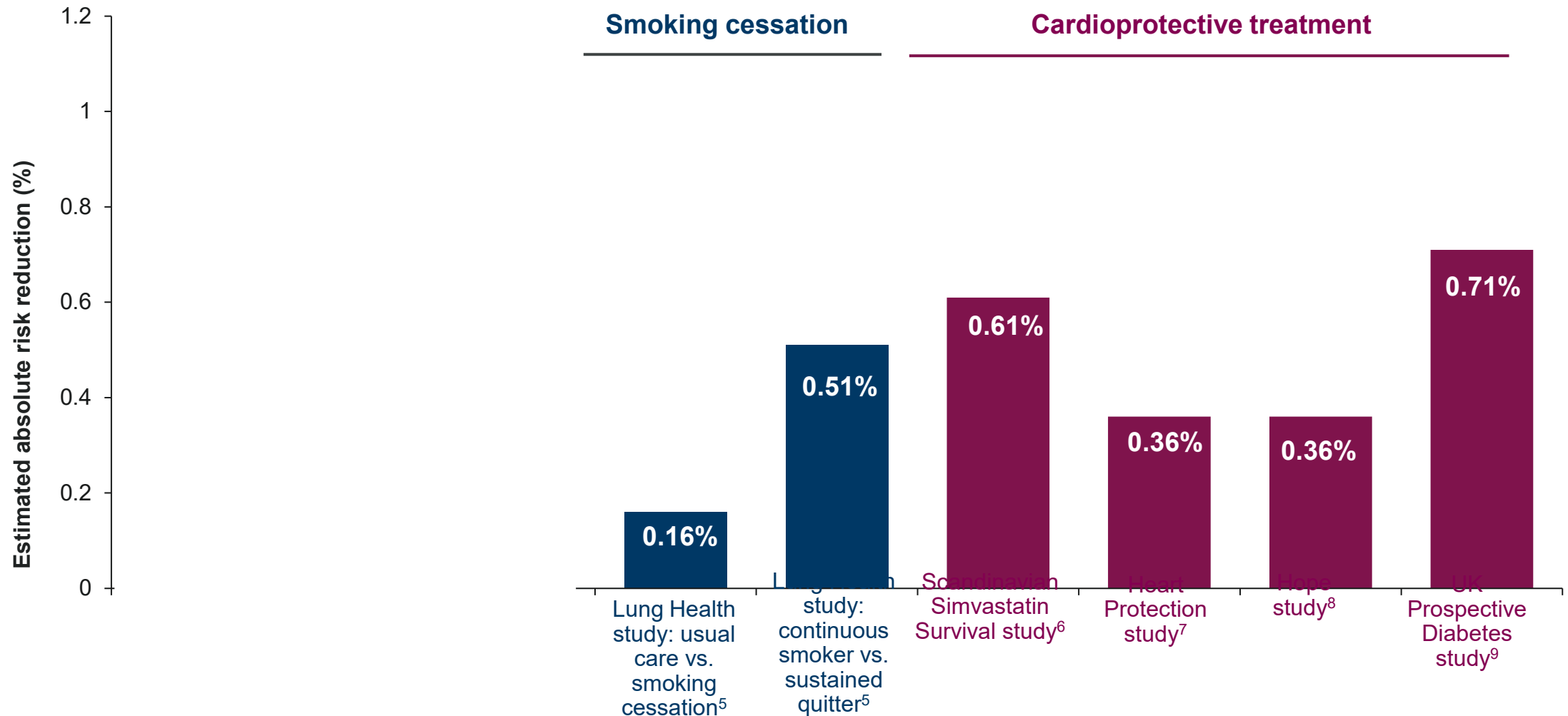
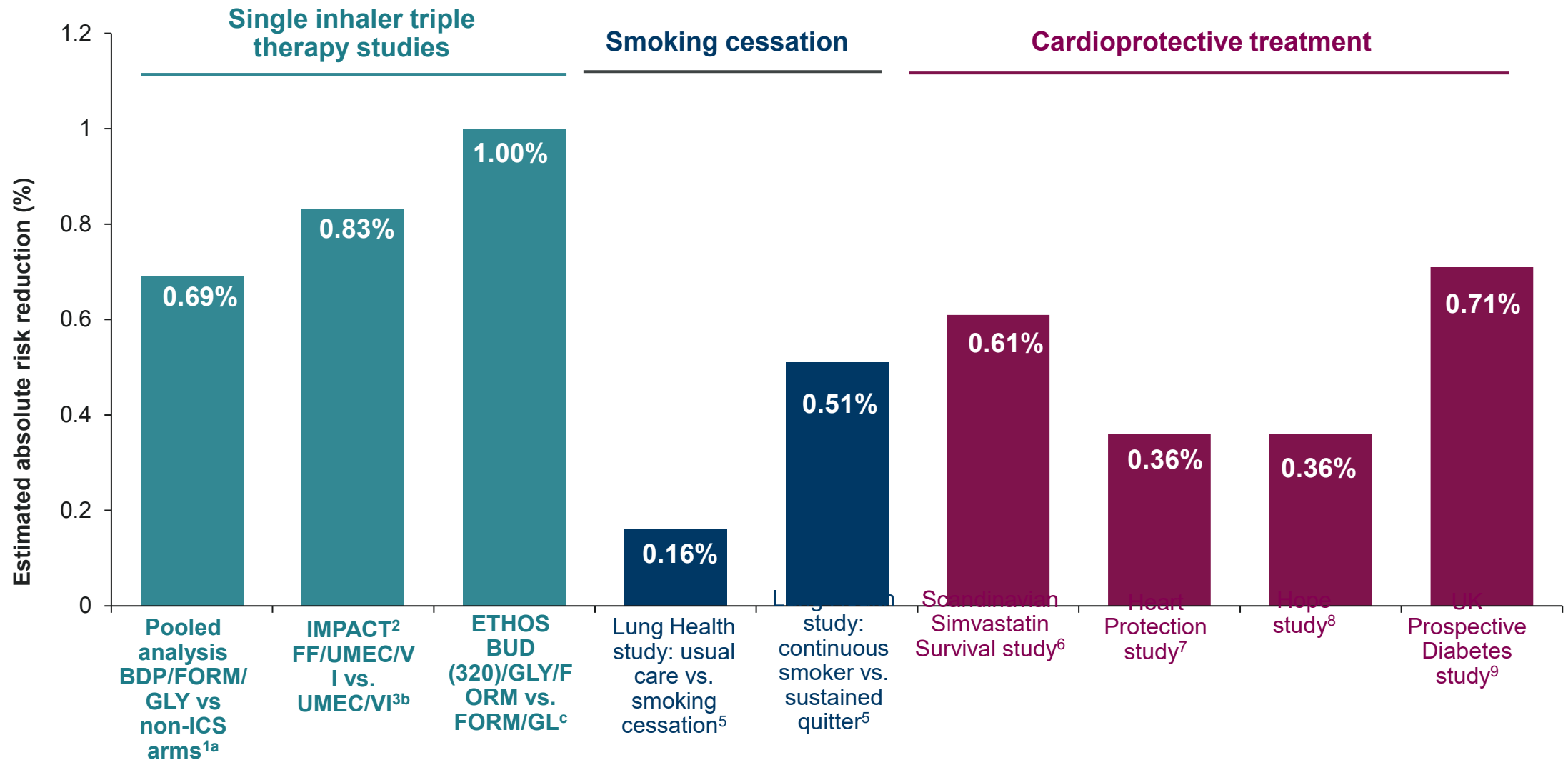**Table 1.** Main characteristics of the clinical studies on COPD in which ACM was included among the outcomes.

Trial	Duration, number of patients (N)	Population	ACM rate control	ACM rate active	Risk reduction (95% CI)	Absolute risk reduction overall	Estimated annual risk reduction*
FP/sal *versus* placebo (full ACM dataset as primary outcome)							
TORCH study[15]	3 years, N = 6112	FEV₁ < 60% predicted; mean exacerbations/year 1	Placebo 15.2%	FP/sal 12.6%	17.5% (−0.2, 31.9)	2.6%	0.87%
Tiotropium *versus* placebo (plus current therapy) (full ACM dataset as secondary outcome)							
UPLIFT study[16]	4 years, N = 5993	Postbronchodilator FEV₁ < 70%	Placebo + CT 16.5%	Tiotropium + CT 14.9%	11% (−0.02, 21)	1.6%	0.4%
FF/VI *versus* placebo (full ACM dataset as primary outcome)							
SUMMIT study[17]	Event driven, N = 16,485	FEV₁ 50–70%; high CV risk	Placebo 6.7%	FF/VI 6.0%	12% (−4, 26)	0.7%	n.a.
ICS/LABA *versus* LABA (full ACM dataset as primary outcome)							
OUTPUL study[18]	1 year, N = 18,615	Recovering from acute exacerbation	LABA and/or LAMA 14.3%	ICS/LABA and/or LAMA 11%	17% (3, 28)	3.3%	3.3%
FF/UMEC/VI triple therapy *versus* UMEC/VI (full ACM dataset as secondary outcome)							
IMPACT study[19,20]	1 year, N = 10,355	High symptom burden ⩾1 exacerbation	UMEC/VI 66 (3.19%)	FF/UMEC/VI 98 (2.36%)	28% (1, 47)	0.83%	0.83%
BUD/GLY/FOR 320/18/9.6 µg triple therapy *versus* GLY/FOR (full ACM dataset as secondary outcome)							
ETHOS study[21]	1 year, N = 8509	High symptom burden ⩾1 exacerbation	GLY/FOR 49 (2.3%)	BUD/GLY/FOR 320/18/9.6 µg 28 (1.3%)	46% (13, 66)	1.0%	1.0%

*Calculated as the ratio of absolute risk reduction and duration of the trial

All-cause mortality benefits of smoking cessation and cardioprotective treatments

Estimated absolute risk reduction (%)

Smoking cessation

Cardioprotective treatment

- Lung Health study: usual care vs. smoking cessation[5] — 0.16%
- Lung Health study: continuous smoker vs. sustained quitter[5] — 0.51%
- Scandinavian Simvastatin Survival study[6] — 0.61%
- Heart Protection study[7] — 0.36%
- Hope study[8] — 0.36%
- UK Prospective Diabetes study[9] — 0.71%

All-cause mortality benefits with single inhaler triple therapy are similar, or better than, smoking cessation and cardioprotective treatments


Estimated absolute risk reduction (%)

Single inhaler triple therapy studies
- Pooled analysis BDP/FORM/GLY vs non-ICS arms[1a]: 0.69%
- IMPACT[2] FF/UMEC/VI vs. UMEC/VI[3b]: 0.83%
- ETHOS BUD (320)/GLY/FORM vs. FORM/GL[c]: 1.00%

Smoking cessation
- Lung Health study: usual care vs. smoking cessation[5]: 0.16%
- Lung Health study: continuous smoker vs. sustained quitter[5]: 0.51%

Cardioprotective treatment
- Scandinavian Simvastatin Survival study[6]: 0.61%
- Heart Protection study[7]: 0.36%
- Hope study[8]: 0.36%
- UK Prospective Diabetes study[9]: 0.71%

Can triple therapy reduce patient mortality?

- **YES!**: EVEN IN THOSE SHOWING "ONLY" ≥1 moderate /severe exacerbation/year

If so, how?

- MAINLY BY REDUCING THE BURDEN OF CARDIOCIRCULATORY EVENTS (during and in-between exacerbations)
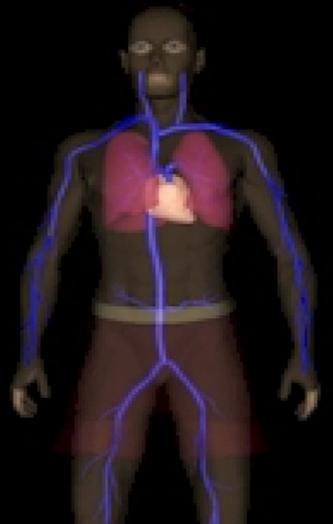
How these pieces of information have advanced the field:
THE 4 TAKE-HOME MESSAGES

- **We should improve our ability to uncover under-reported exacerbations**

- **We may need to re-think the definition of "high-risk" patient: even a modest burden of exacerbations matters relative to mortality!**

- **We should be more proactive to identify patients with the greatest burden of cardiocirculatory comorbidities**

- **If we act sooner rather than later with triple therapy we can improve survival in these patients, mainly by reducing the cardiovascular risk**

Thanks for your attention !

Queen's University / Kingston General Hospital
Kingston, ON, Canada