Are we doing too little too late in COPD management?

Can we more effectively manage COPD symptoms?

Can we more effectively manage COPD exacerbation?

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Date of production:2019/Nov/28th

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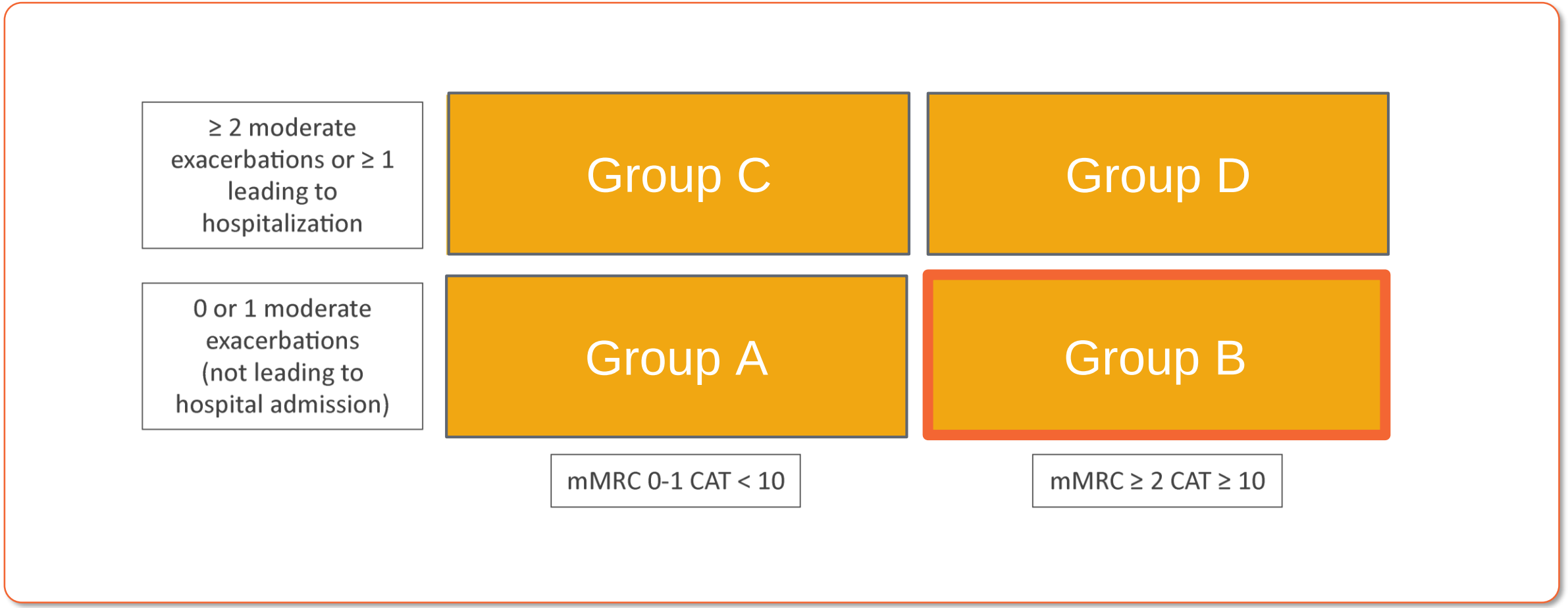
GOLD 2019 Assessment scheme

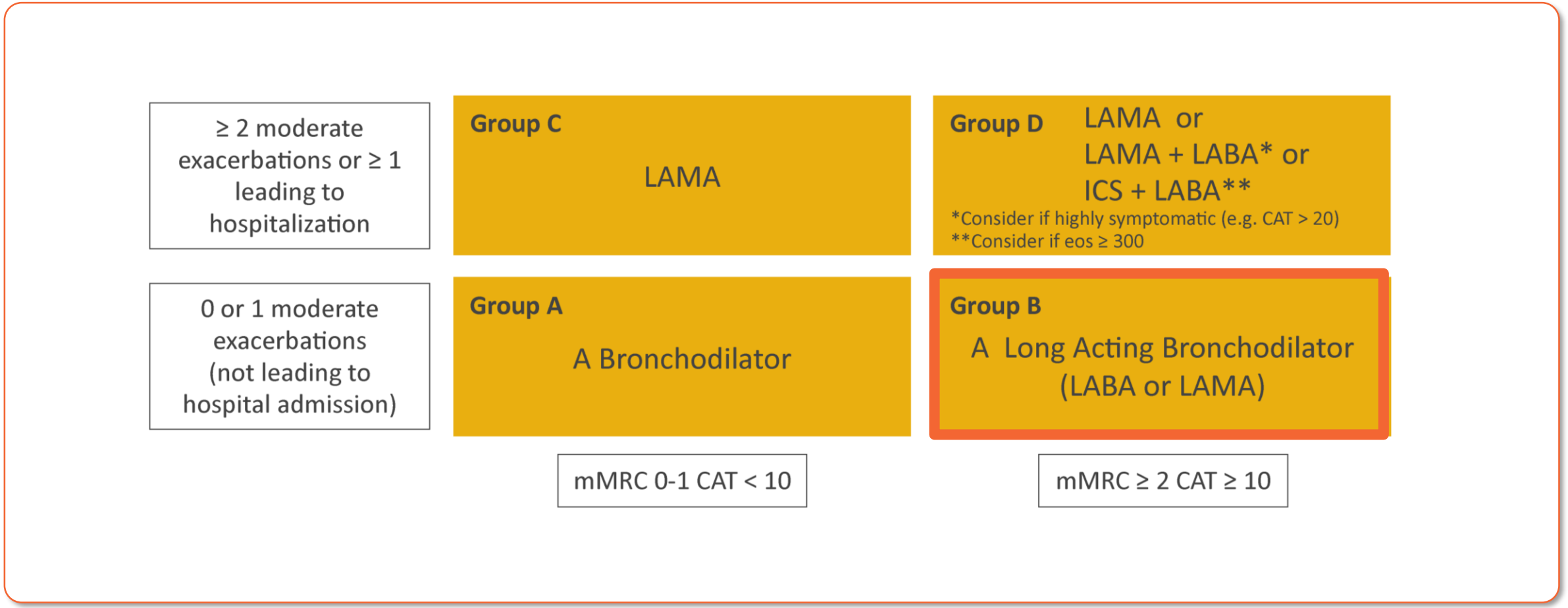


Adapted from: GOLD 2019

Clinical QUESTIONS

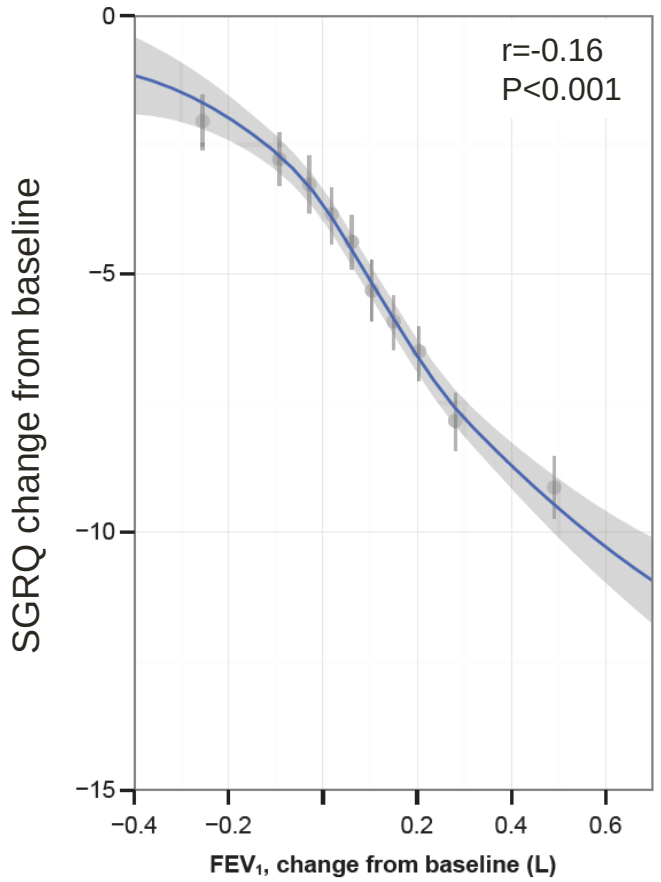
1. **Who** are the right patients for dual-bronchodilators?
2. **Who** are the right patients for triple therapy?
3. **What** benefit will our patients get from triple therapy?
4. **Do** the benefits of triple therapy outweigh the risks?
5. **When** should we treat? Early or step up over time?

GOLD 2019 Initial Pharmacological Treatment



Adapted from: GOLD 2019

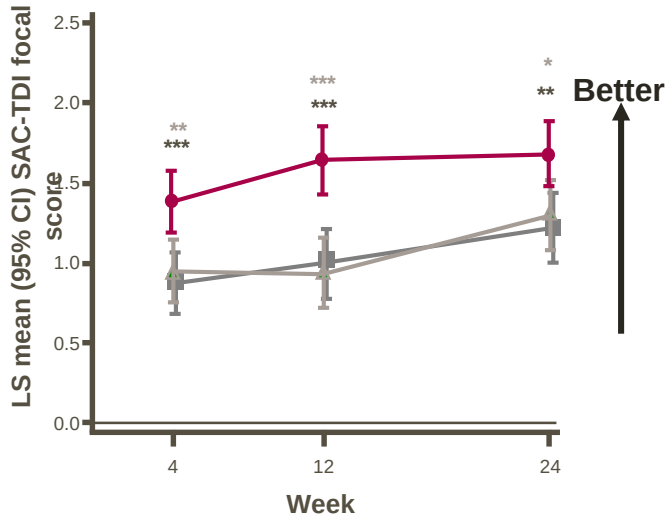
Pooled analysis (Loess curves) of the relationship between change in FEV_1 and change in SGRQ score: 23 trials with 23,213 patients



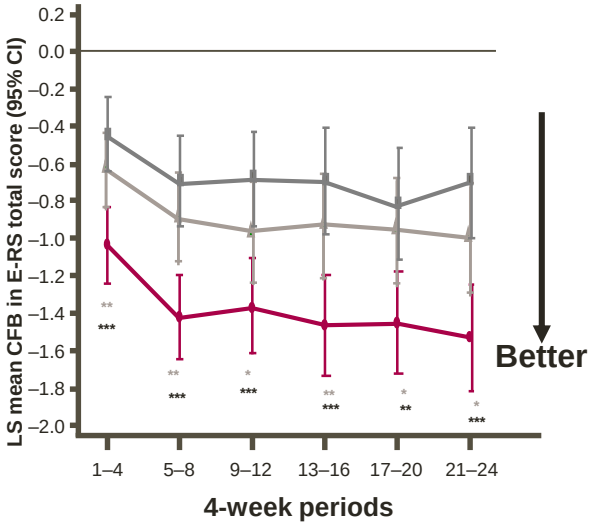
Donohue JF, et al. Pulm Pharmacol Ther. 2018 Apr;49:11-19.

Breathlessness, daily symptoms and rescue-free days with better UMEC/VI vs LAMA or LABA monotherapy

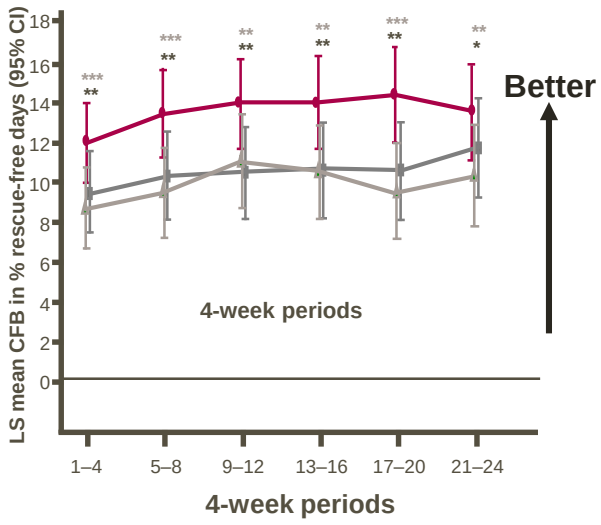
Breathlessness (SAC-TDI)



Daily symptom burden (E-RS total score)



Rescue-free days

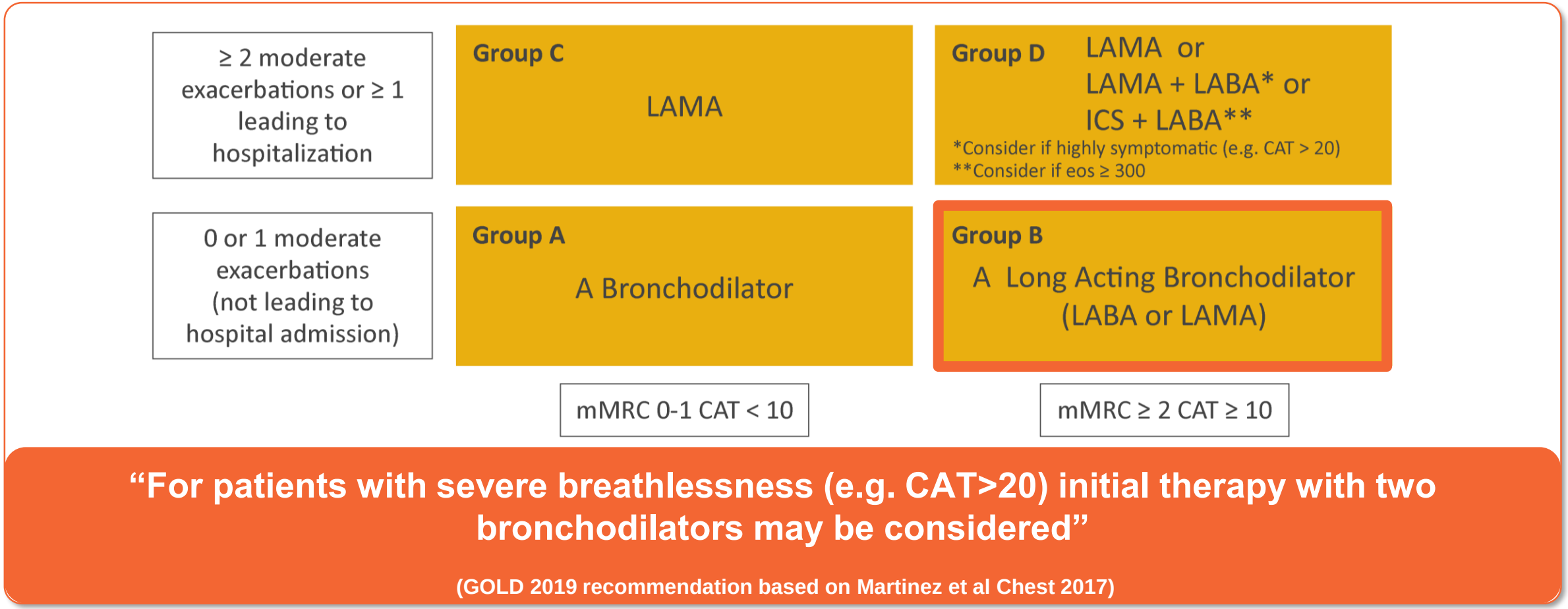


UMEC/VI 62.5/25 µg QD UMEC 62.5 µg QD SAL 50 µg BID

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$ **UMEC/VI** vs **UMEC**
*** $p < 0.001$, ** $p < 0.01$ **UMEC/VI** vs **SAL**

Maltais et al. Respiratory Research (2019) 20:238
)

GOLD 2019 Initial Pharmacological Treatment

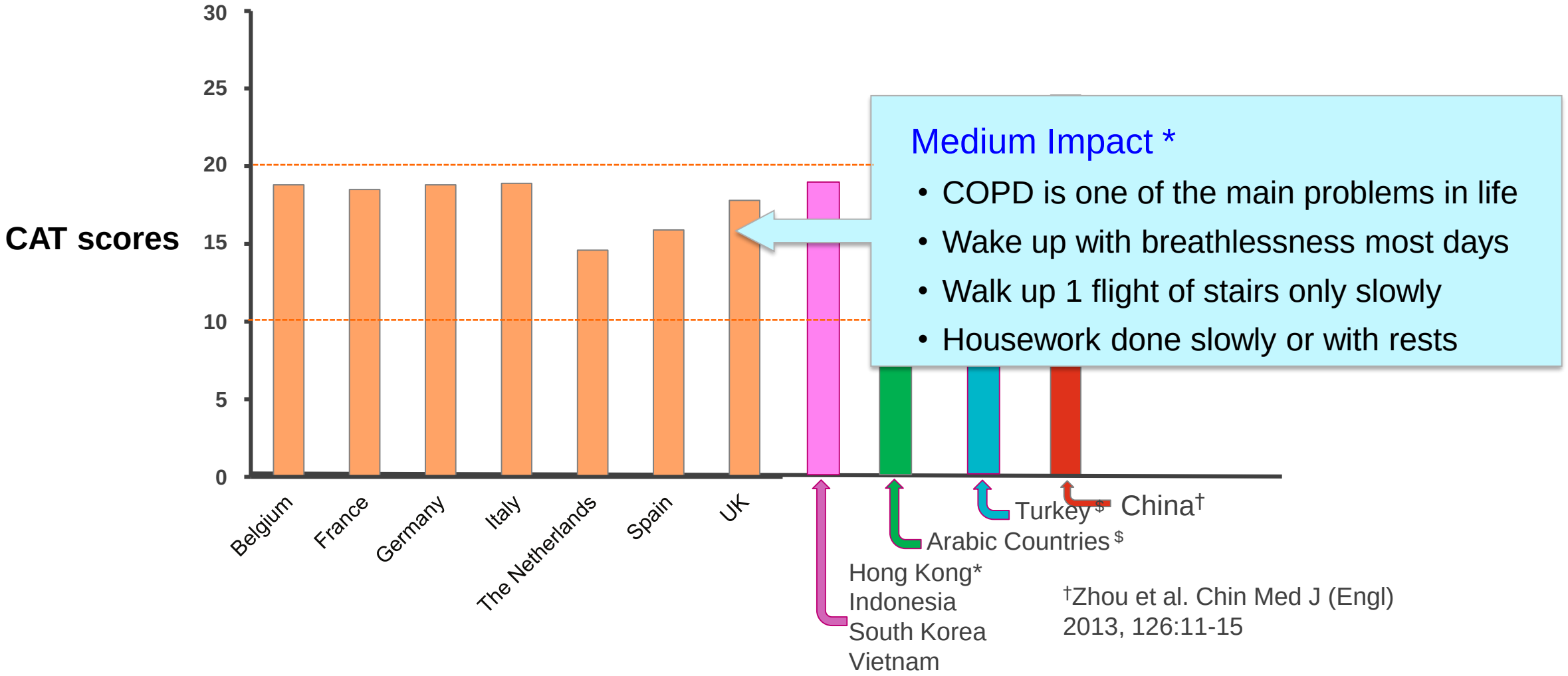


"For patients with severe breathlessness (e.g. CAT>20) initial therapy with two bronchodilators may be considered"

(GOLD 2019 recommendation based on Martinez et al Chest 2017)

Adapted from: GOLD 2019

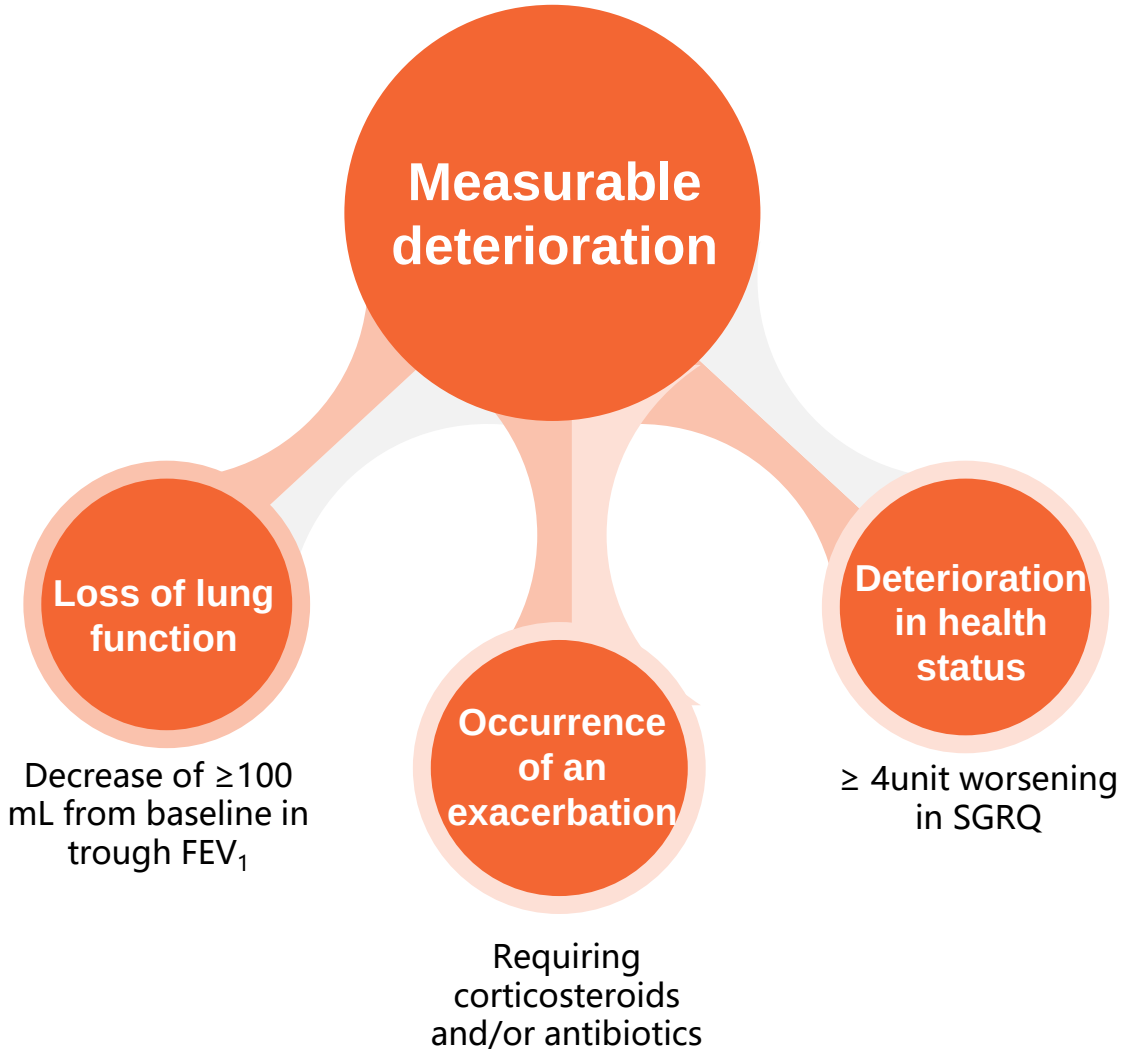
CAT scores across the world



*Based on CAT scenarios in: Jones et al BMC Pulmonary Medicine. 2011;11(1):42

Jones et al Eur Respir J 2011; 38: 29–35; *Kwon et al Chest 2013; 143:703-710; $Jones et al. Respir Med 2012, 106 Suppl 2:S86-99

A composite approach to assess short-term worsening (clinical stability) in COPD



One or more of these is a clinically important deterioration (CID)

Naya IP, et al. Respir Res. 2018 Nov 20;19(1):222.

Eclipse study: Composite endpoint (CID) at 6 months as a predictor of outcomes after 3 years

1st moderate/severe exacerbation

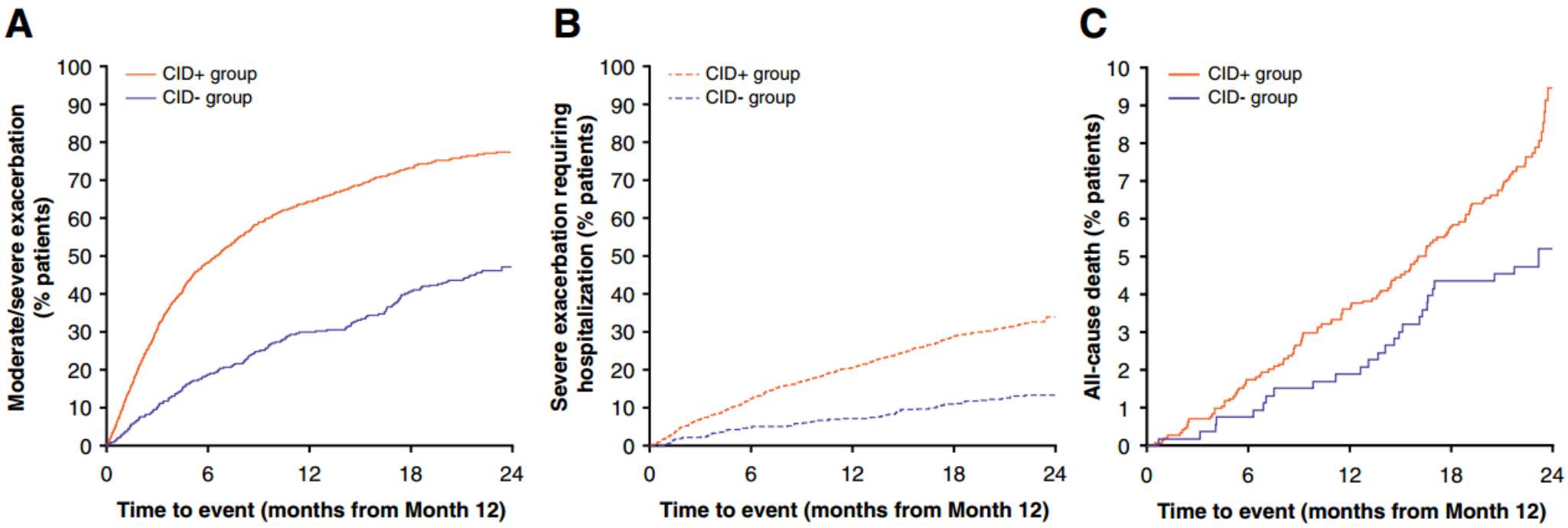
HR 2.54 (95% CI 2.20, 2.93)

1st severe exacerbation

HR 2.81 (95% CI 2.17, 3.63)

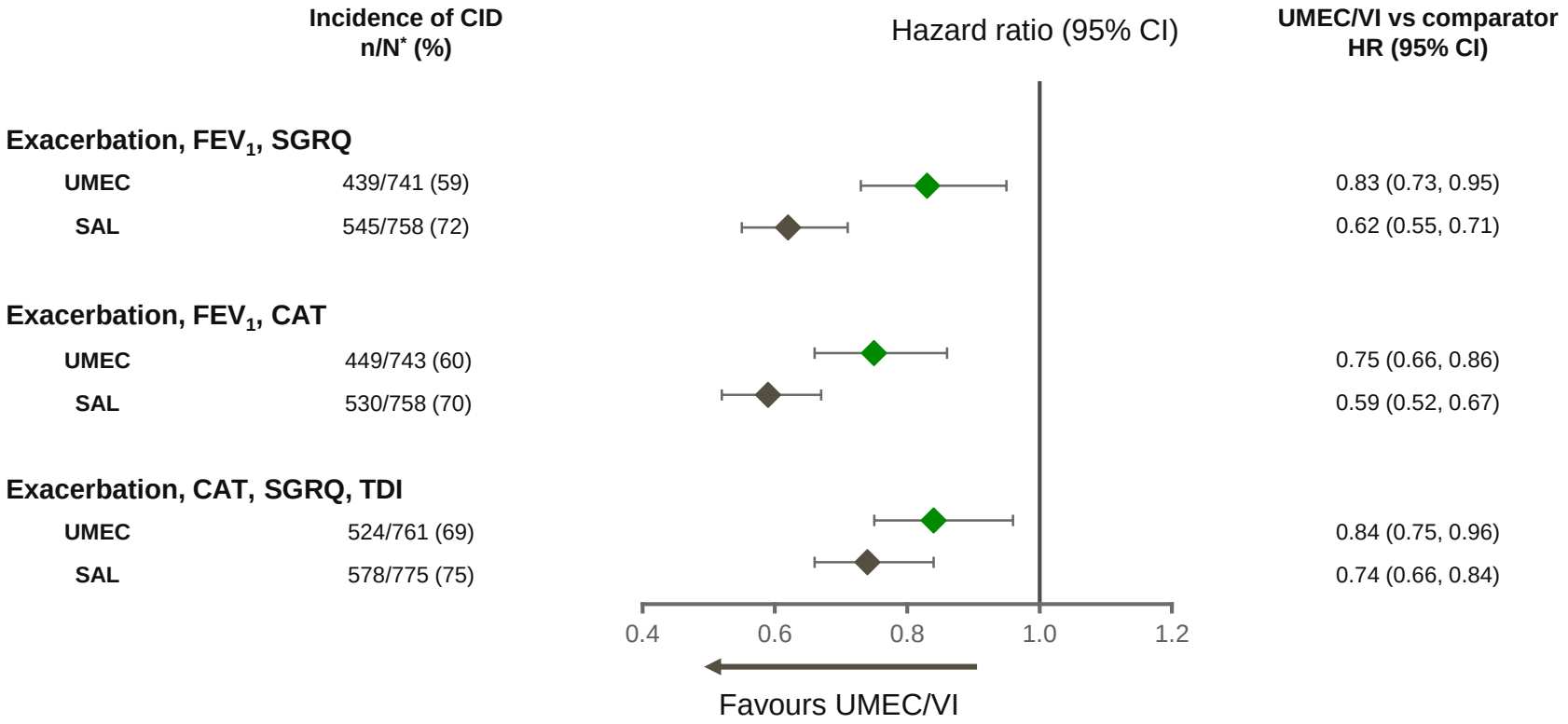
All cause mortality

HR 1.59 (95% CI 1.04, 2.41)



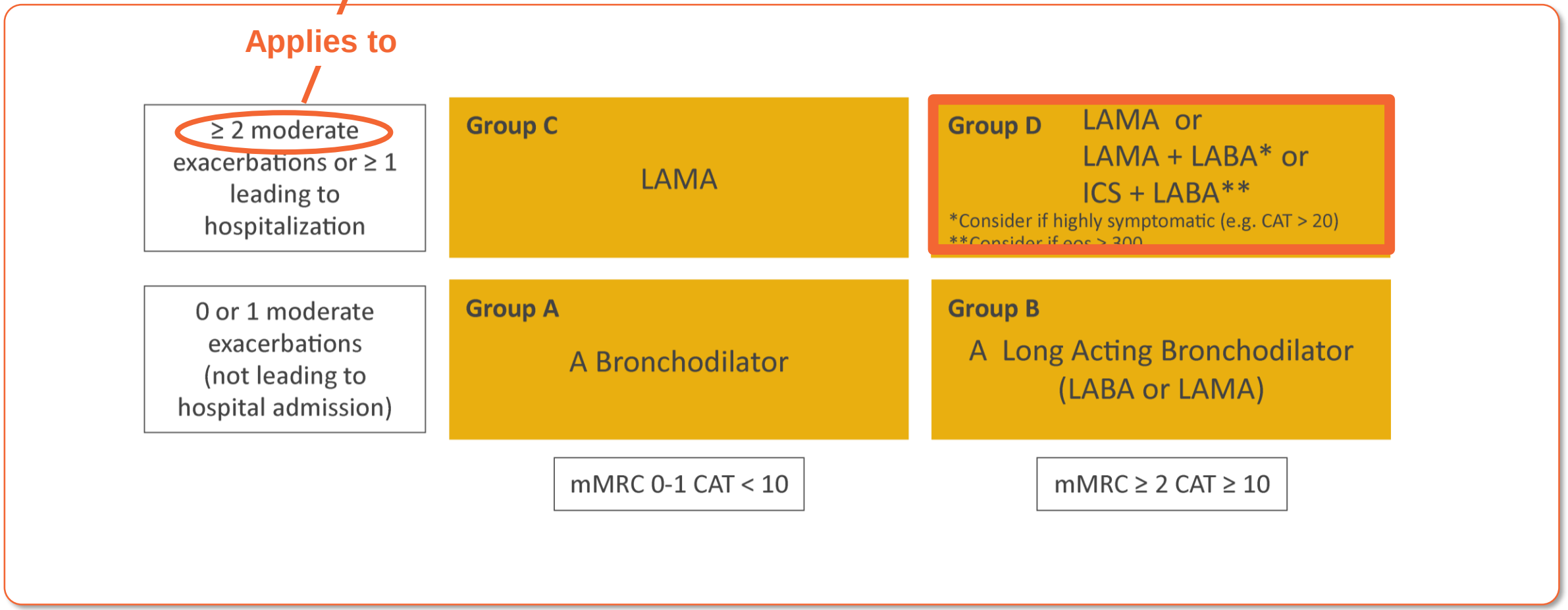
Naya IP, et al. Respir Res. 2018 Nov 20;19(1):222.

Greater stability at 6 months on with UMEC/VI than LAMA or LABA alone (using three CID definitions)



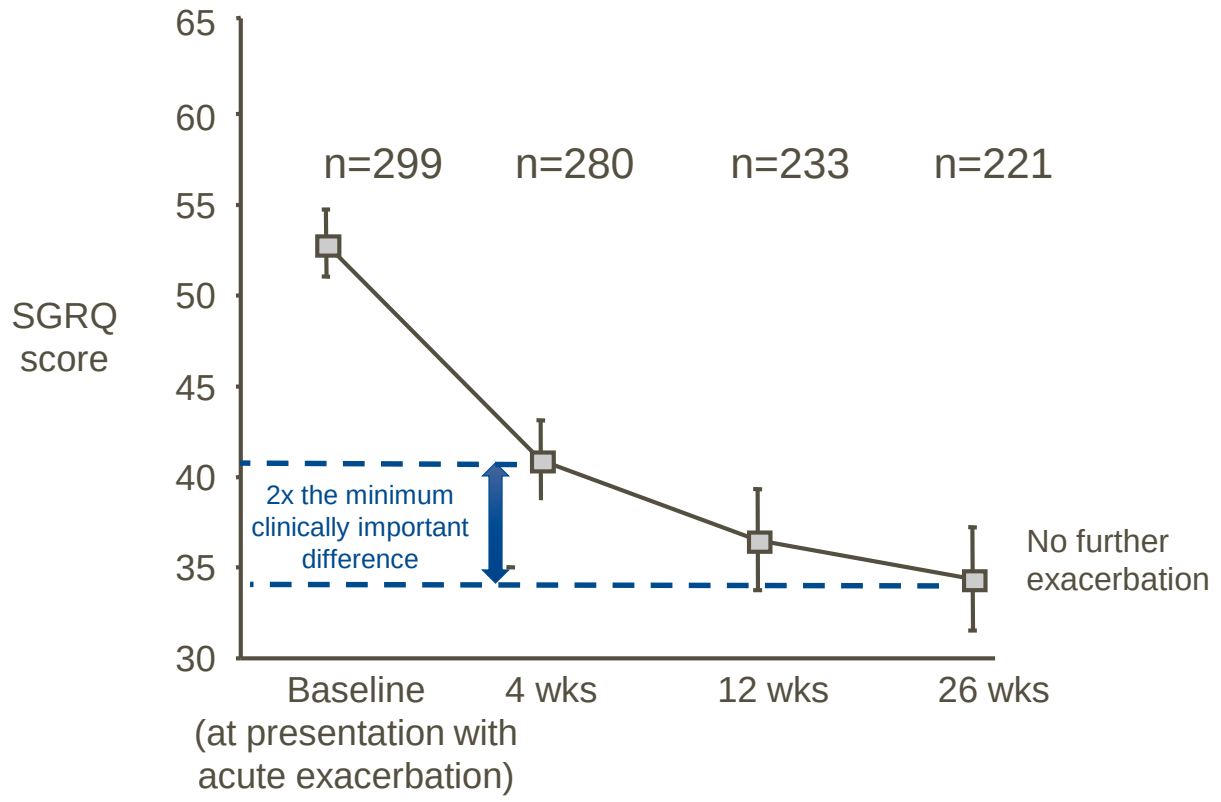
Vogelmeier et al. ATS 2019. #A3315/P504.

GOLD 2019 Initial Pharmacological Treatment



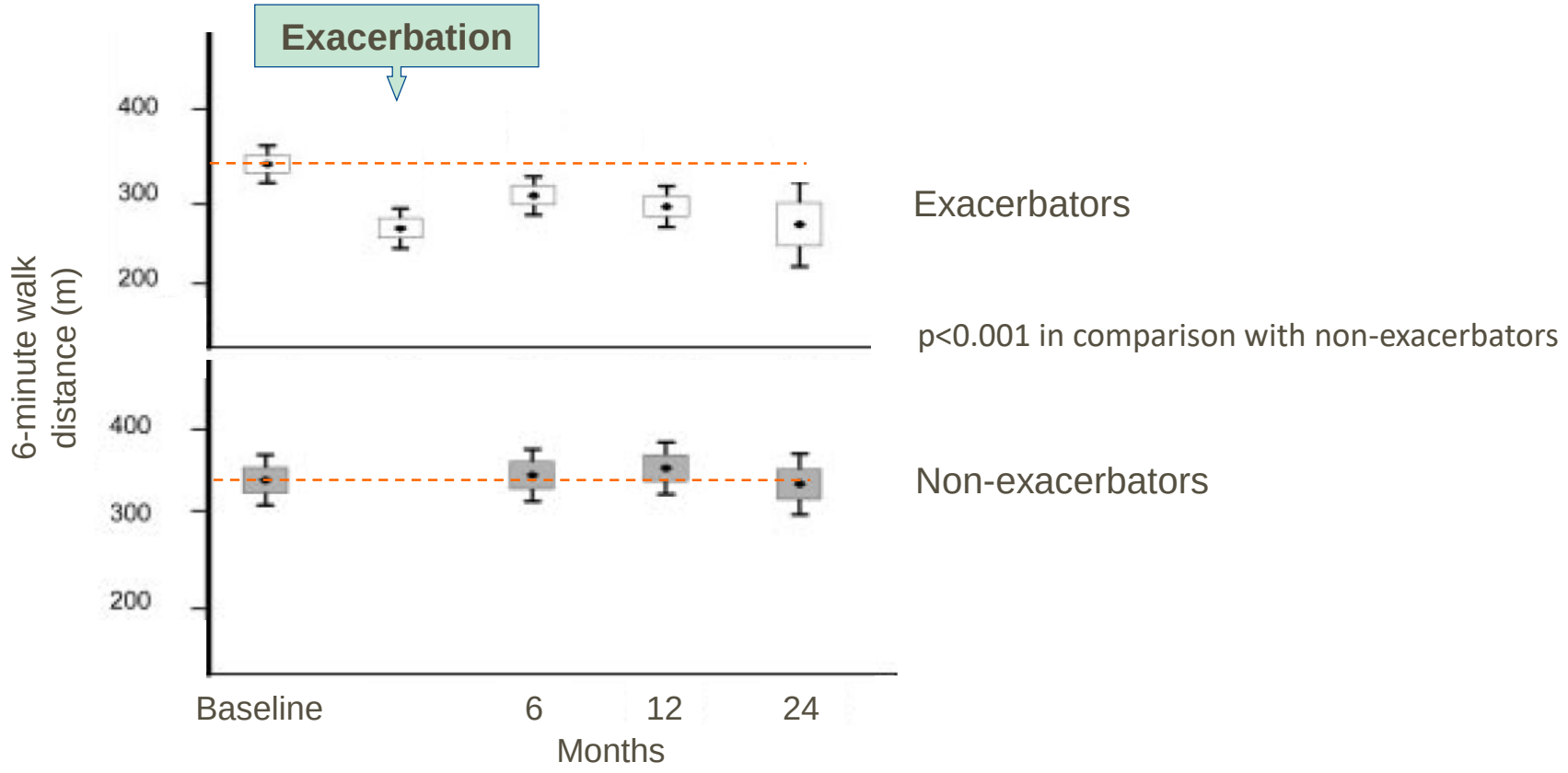
Adapted from: GOLD 2019

Health status changes following an exacerbation (GOLD Stage 2 patients)



Adapted from:Spencer & Jones. 2003 Jul;58(7):589-93.

Effect of one exacerbation on 6-minute walk distance

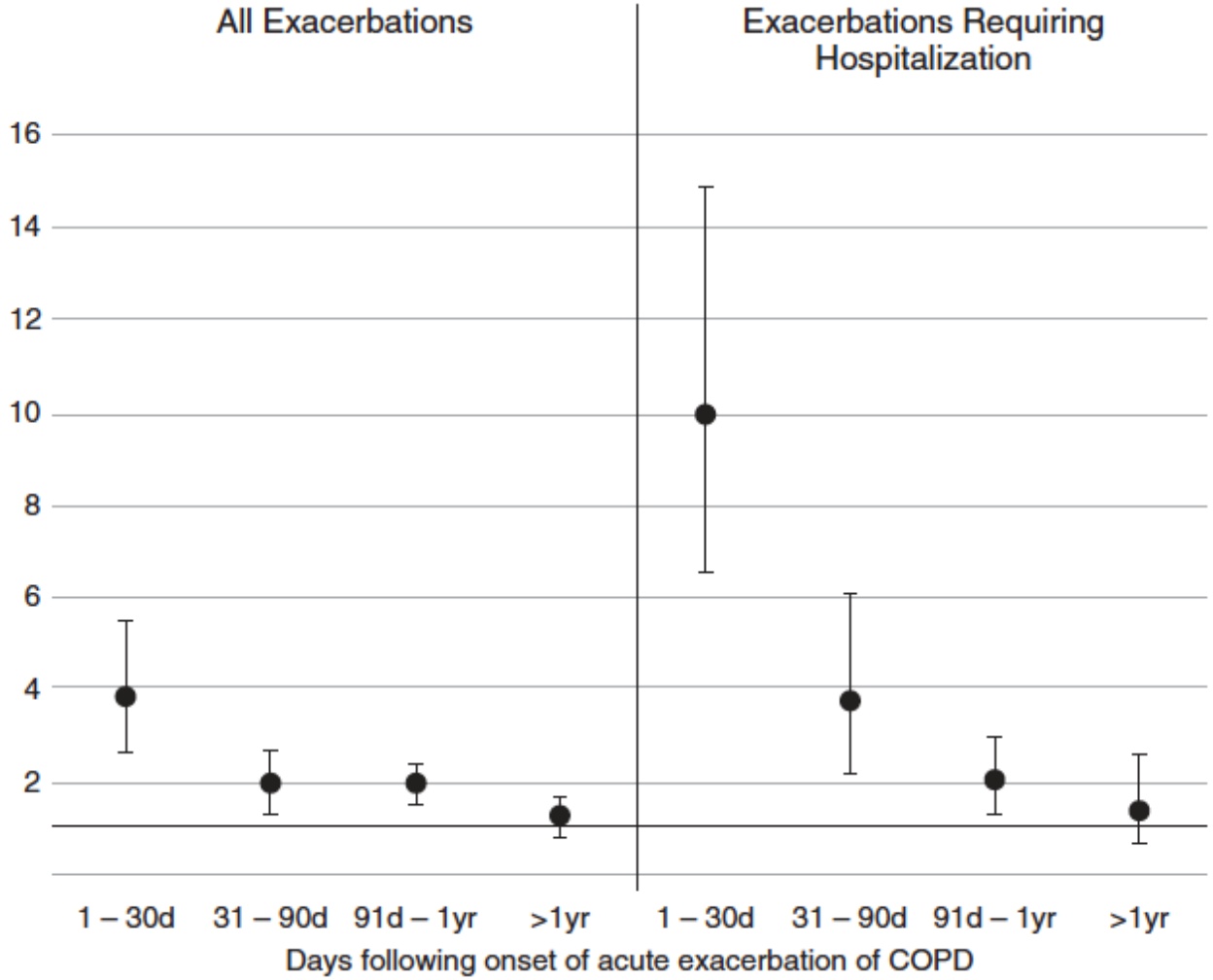


Cote et al. CHEST. 2007 Mar;131(3):696-704.

Acute cardiovascular events following an exacerbation

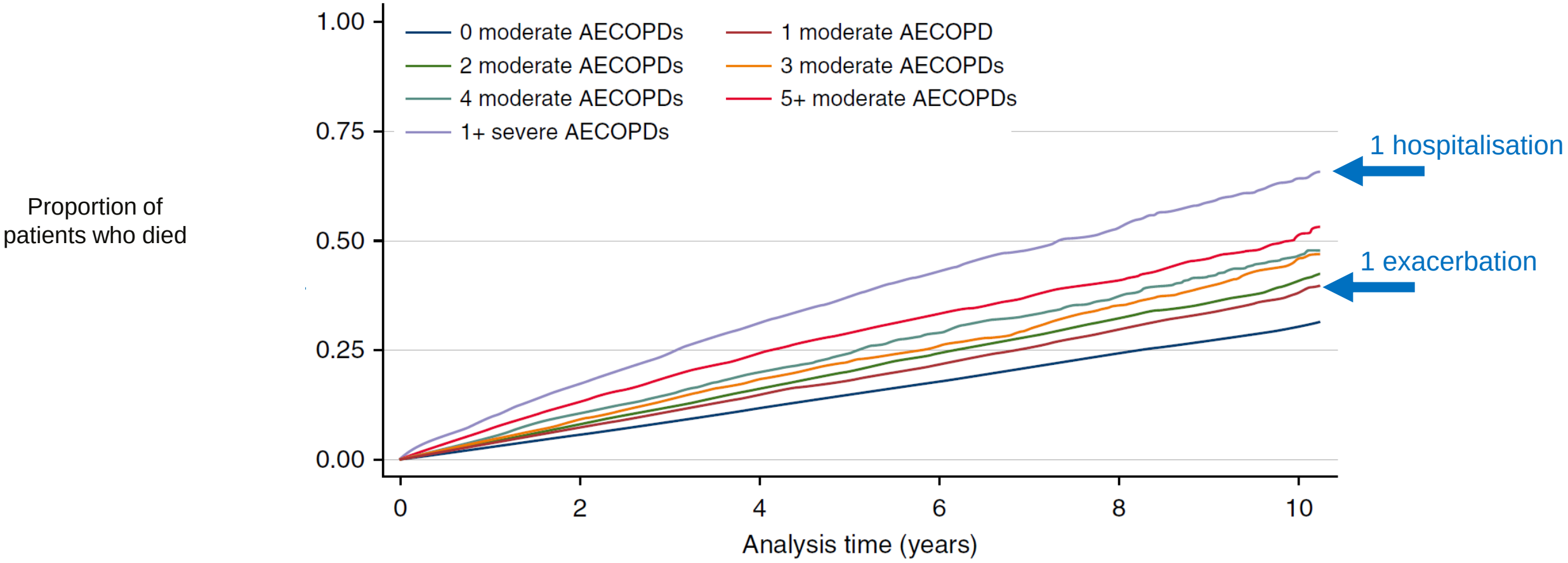
- Cardiovascular death
- Myocardial infarction
- Stroke
- Unstable angina
- Transient ischemic attack

Hazard ratios for cardiovascular event



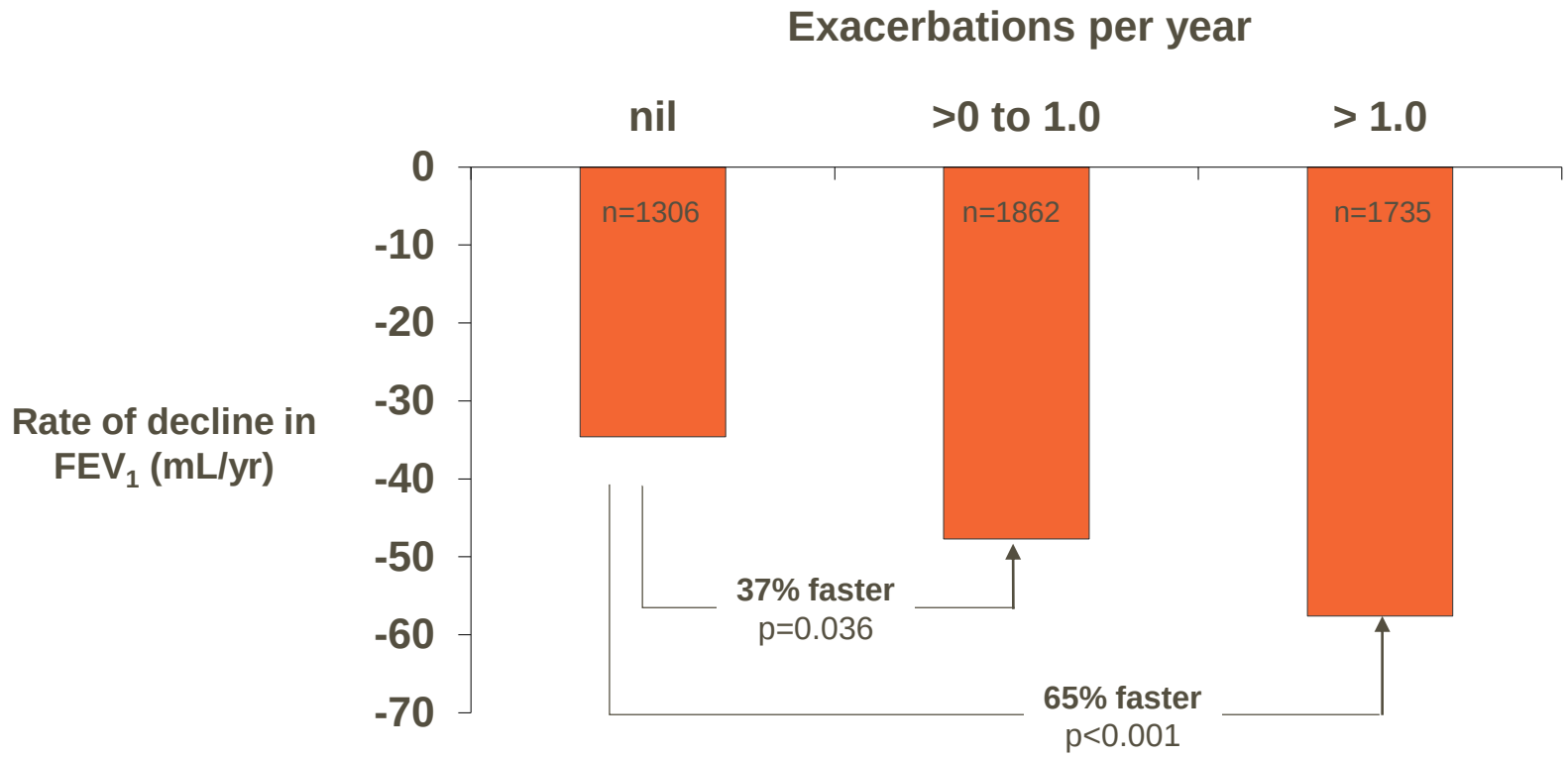
Kunisaki et al Am J Respir Crit Care Med; 2018; 198: 51–57

Exacerbations (AECOPD) and risk of death



Adapted from Rothnie KJ, et al. Am J Resp Crit Care Med. 2018;198:464−471.

TORCH study: Exacerbation rate and FEV_1 decline (all treatment arms combined)



Adjusted for smoking status, gender, baseline FEV_1, region, BMI, prior exacerbations, treatment, time, time by treatment and covariate by time

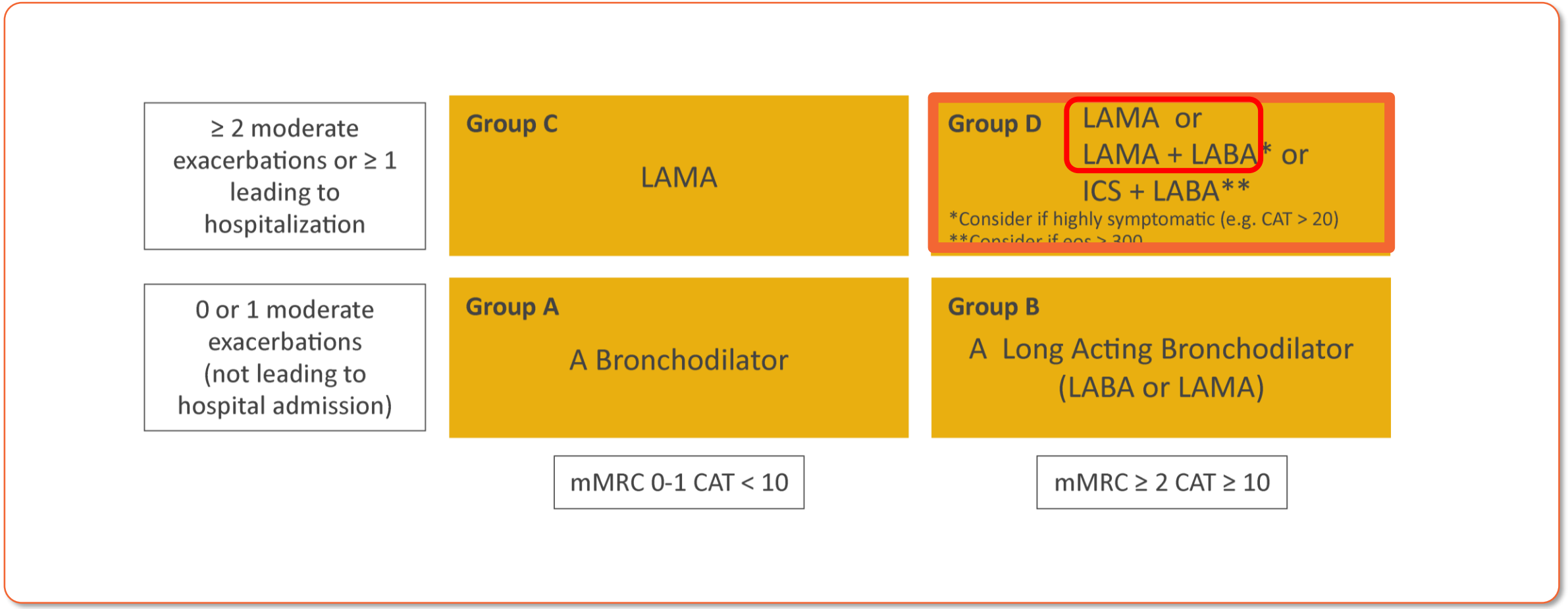
Adapted from: Celli et al Am J Respir Crit Care Med. 2008 Aug 15;178(4):332-8 (Calculated from Table 5)

Complications following short-course of systemic corticosteroids given for respiratory conditions within the preceding 5−30 days (self-controlled study)

Adverse event	Incidence rate ratio (95% CI, 5-30 days)	*p* value
Sepsis	3.8 (1.9−7.4)	<0.001
Venous thromboembolism	3.1 (2.2−4.4)	<0.001
Fracture	2.0 (1.6−2.4)	<0.001

Waljee AK, et al. BMJ. 2017;357:j1415.

GOLD 2019 Initial Pharmacological Treatment



Adapted from: GOLD 2019

Efficacy of dual bronchodilator over LAMA alone on moderate/severe exacerbations

Trial	Dual bronchodilator	LAMA	Mean rate difference	Significance
Spark[1]	Glycopyrronium/ indacaterol	Glycopyrronium	12%	p<0.05
Spark[1]	Glycopyrronium/ indacaterol	Tiotropium	10%	p>0.05
Dynagito[2]	Tiotropium/olodaterol	Tiotropium	7%	p=0.0498*

Mean effect of adding LABA ≈10% reduction

*pre-specified significance level p<0.01

1. Wedzicha et al. Lancet Respiratory Medicine 2013, May;1(3):199-209
2. Calverley et al Lancet Respir Med http://dx.doi.org/10.1016/S2213-2600(18)30102-4

Role of dual bronchodilator

Primary role - to improve symptoms

- More effective than LAMA alone
- Chinese COPD patients have a high level of symptoms

Small effect on exacerbations

- In addition to LAMA alone

Clinical QUESTIONS

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5. **When** should we treat? Early or step up over time?

License for Trelegy in Taiwan

For the treatment of patients with chronic obstructive pulmonary disease (COPD) not adequately treated with ICS/LABA or LAMA/LABA

肺樂喜易利達92/55/22 mcg乾粉吸入劑
TRELEGY ELLIPTA 92/55/22 mcg Inhalation Powder

衛部藥輸字第027395號
本藥須由醫師處方使用

1 適應症與用途

TRELEGY ELLIPTA是一種吸入性的皮質類固醇/抗膽鹼激性藥物/長效型β_2腎上腺素作用劑複方製劑，適用於已接受吸入性皮質類固醇與長效β_2作用劑合併治療，仍然有顯著症狀或惡化(exacerbations)控制不佳之慢性阻塞性肺病(COPD)患者的維持治療。

重要使用限制

TRELEGY ELLIPTA並不適用於緩解急性支氣管痙攣或治療氣喘。

2 用法用量

TRELEGY ELLIPTA應以每天吸入一次的方式投藥，且僅可經口吸入。吸入之後，患者應用水漱口，且不可吞下，這是為了幫助降低發生口咽念珠菌病的風險。TRELEGY ELLIPTA應每天於相同時間投藥。

每24小時不可使用TRELEGY ELLIPTA超過1次。對老年患者、腎功能不全患者或中度肝功能不全患者，都不須調整劑量。

3 CONTRAINDICATIONS

- 有嚴重乳蛋白過敏問題。
- 已證實對fluticasone furoate、umeclidinium、vilanterol或任何賦形劑過敏。

4 警語和注意事項

一項針對氣喘患者所進行的大型安慰劑對照試驗的資料顯示，LABA可能會升高發生氣喘相關死亡的風險。

5 不良反應

LABA (如vilanterol，TRELEGY ELLIPTA的活性成分之一)會升高發生氣喘相關死亡的風險。TRELEGY ELLIPTA並不適用於治療氣喘。

- 白色念珠菌感染
- COPD患者發生肺炎的風險升高
- 免疫抑制
- 腎上腺皮質功能亢進與腎上腺抑制
- 反常性支氣管痙攣
- 心血管影響
- 骨質密度降低
- 狹角性青光眼惡化
- 尿滯留惡化

•不良事件通報程序：通報電話: (02) 23126836/ 郵箱: oax40892@gsk.com
•詳細處方資訊備索

葛蘭素史克藥廠 地址:100台北市忠孝西路一段66號24樓

安肺樂易利達 55/22 mcg 乾粉吸入劑 簡易仿單資訊

ANORO ELLIPTA 55/22 mcg Inhalation Powder

衛部藥輸字第 026315 號

1. 適應症與用途

ANORO ELLIPTA 是一種抗膽鹼激性藥物/長效型β_2腎上腺素作用劑(anticholinergic/LABA) 複方製劑，適用於以長期每日使用一次的方式做為慢性阻塞性肺病(COPD)患者之氣道阻塞症狀的維持治療用藥。ANORO ELLIPTA 並不適用於緩解急性支氣管痙攣或治療氣喘。

2. 用法用量

ANORO ELLIPTA (umeclidinium/vilanterol 55 mcg/22 mcg)(遞送劑量)應以每天吸入一次的方式投藥，且僅可經口吸入。每天應於相同時間投藥。每 24 小時不可使用 ANORO ELLIPTA 超過 1 次。

3. 禁忌

ANORO ELLIPTA 禁用於有嚴重乳蛋白過敏問題的患者，或已證實對 umeclidinium、vilanterol 或任何賦形劑過敏的患者。

4. 警語和注意事項

- 發生氣喘相關死亡之風險升高的現象一般認為是一種 LABA (包括 vilanterol，即 ANORO ELLIPTA 的活性成分之一)的類別作用。目前尚未進行過任何足以判定在使用 ANORO ELLIPTA 治療之患者中，氣喘相關死亡率是否會升高的研究。ANORO ELLIPTA 用於氣喘患者的安全性與療效尚未確立因此並不適用於治療氣喘。可能導致病情惡化與急性發作
- 不可過度使用 ANORO ELLIPTA 及與其他長效型β_2作用劑併用
- 低血鉀與高血糖

5. 不良反應

- 反常性支氣管痙攣
- 心血管影響
- 狹角性青光眼惡化
- 尿滯留惡化

不良事件通報程序： 通報電話: (02) 23126836/ 電子信箱: oax40892@gsk.com
詳細處方資訊備索
公司名稱 :葛蘭素史克藥廠
公司地址: 台北市忠孝西路一段 66 號 24 樓

Clinical QUESTIONS

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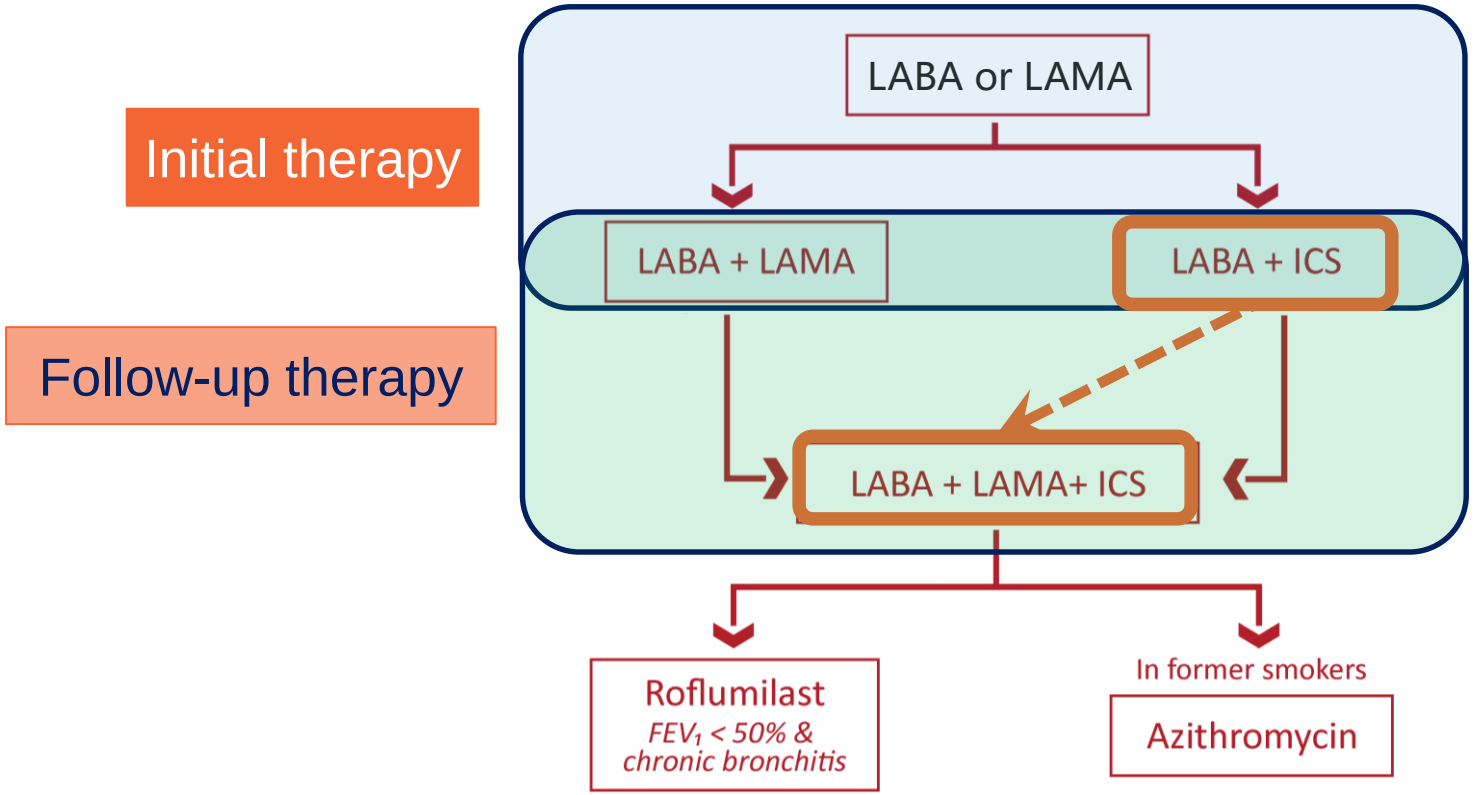
Trelegy benefits - exacerbations

Follow up Pharmacological Treatment- exacerbations

Pathway for a patient who has an exacerbation despite 1st choice treatment

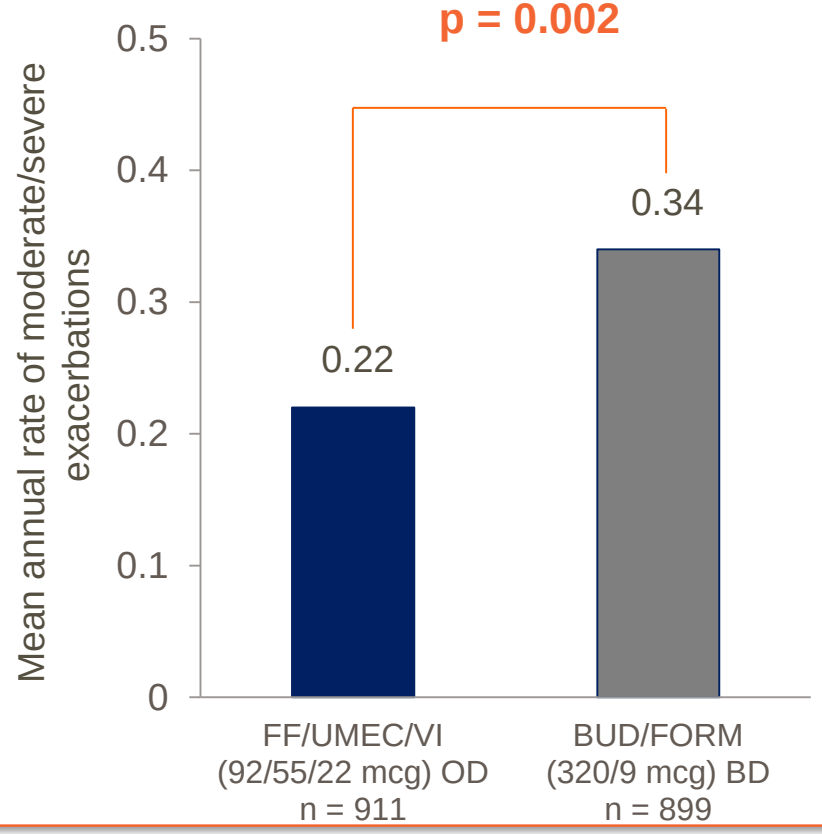


Adapted from: GOLD 2019

FULFIL study: Moderate-severe exacerbations for Trelegy Ellipta OD vs BUD/FOR Tubuhaler BD

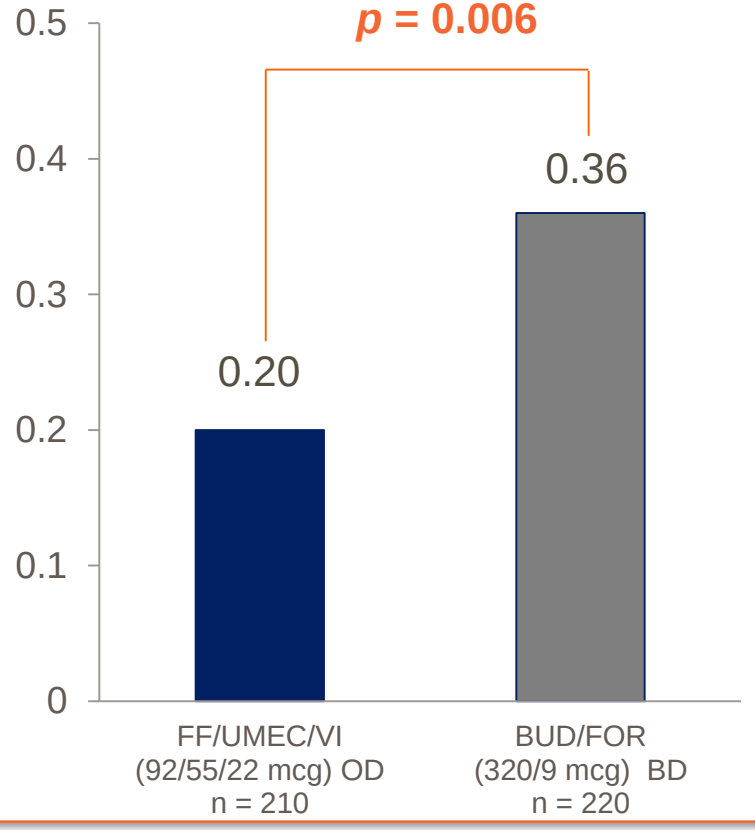
ITT population (24 weeks)

Reduction: 35% (95% CI: 14, 51)
p = 0.002



Extension population (52 weeks)

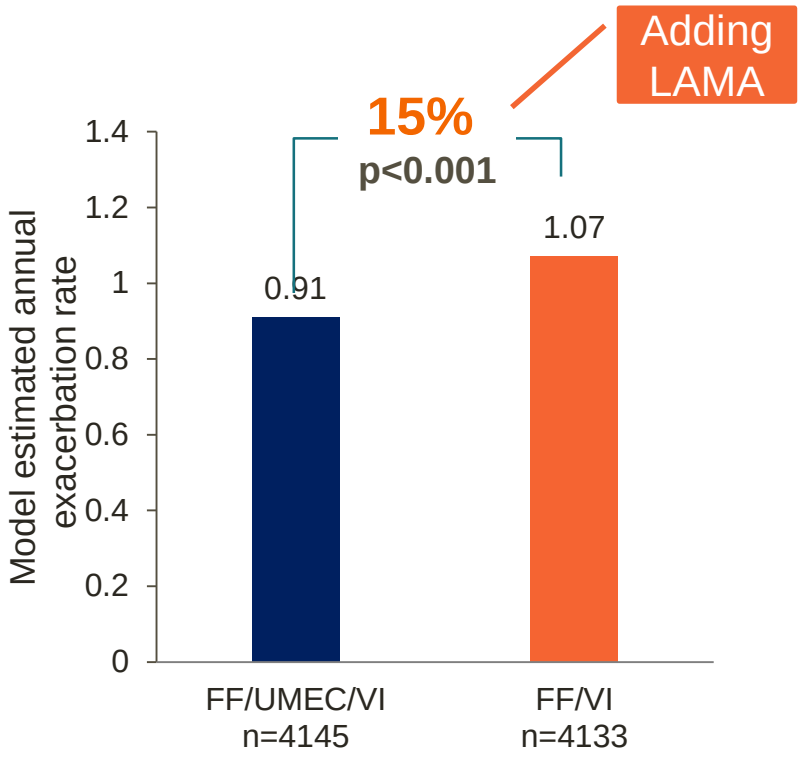
Reduction: 44% (95% CI: 15, 63)
***p* = 0.006**



Moderate exacerbation - worsening symptoms of COPD requiring treatment with oral/systemic corticosteroids and/or antibiotics.
Severe exacerbation - worsening symptoms of COPD that required treatment with inpatient hospitalisation.

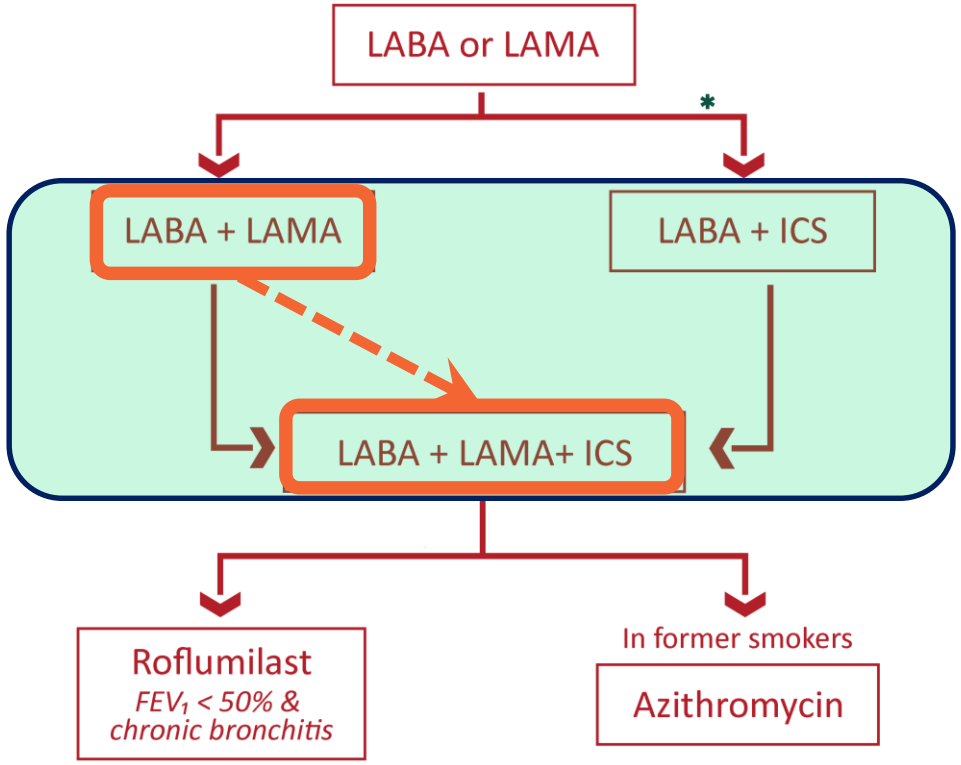
Adapted from Lipson DA,et al. Am J Respir Crit Care Med. 2017 Aug 15;196(4):438-446., Trelegy Ellipta SmPC 2017 (Draft), Symbicort Turbohaler SmPC 2017

IMPACT study: reduction in annual rate of moderate/severe exacerbations with FF/UMEC/VI vs ICS/LABA and vs LAMA/LABA



Adapted from: Lipson DA, et al. N Engl J Med. 2018 May 3;378(18):1671-1680.

Follow up Pharmacological Treatment- exacerbations



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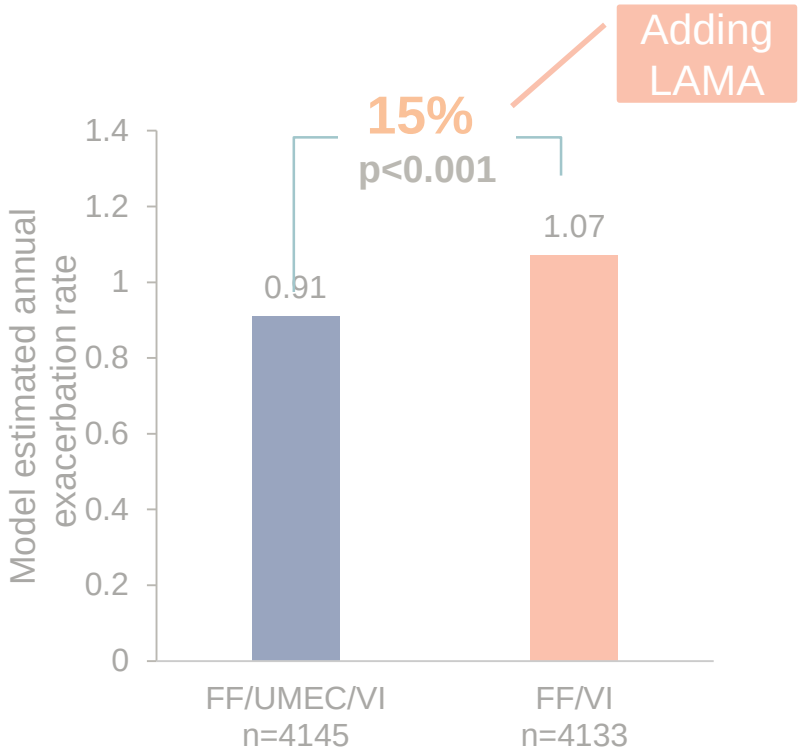
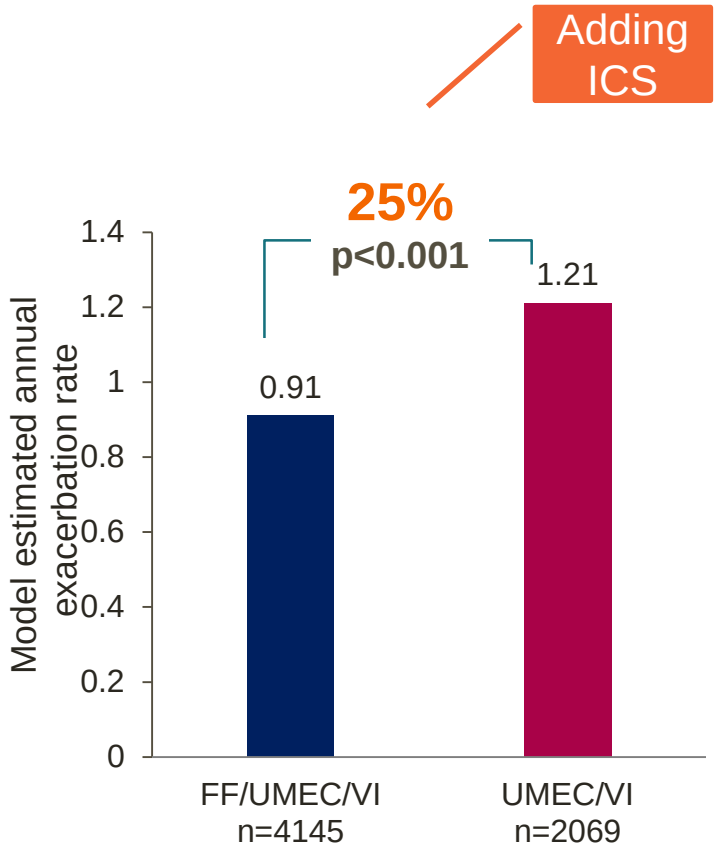
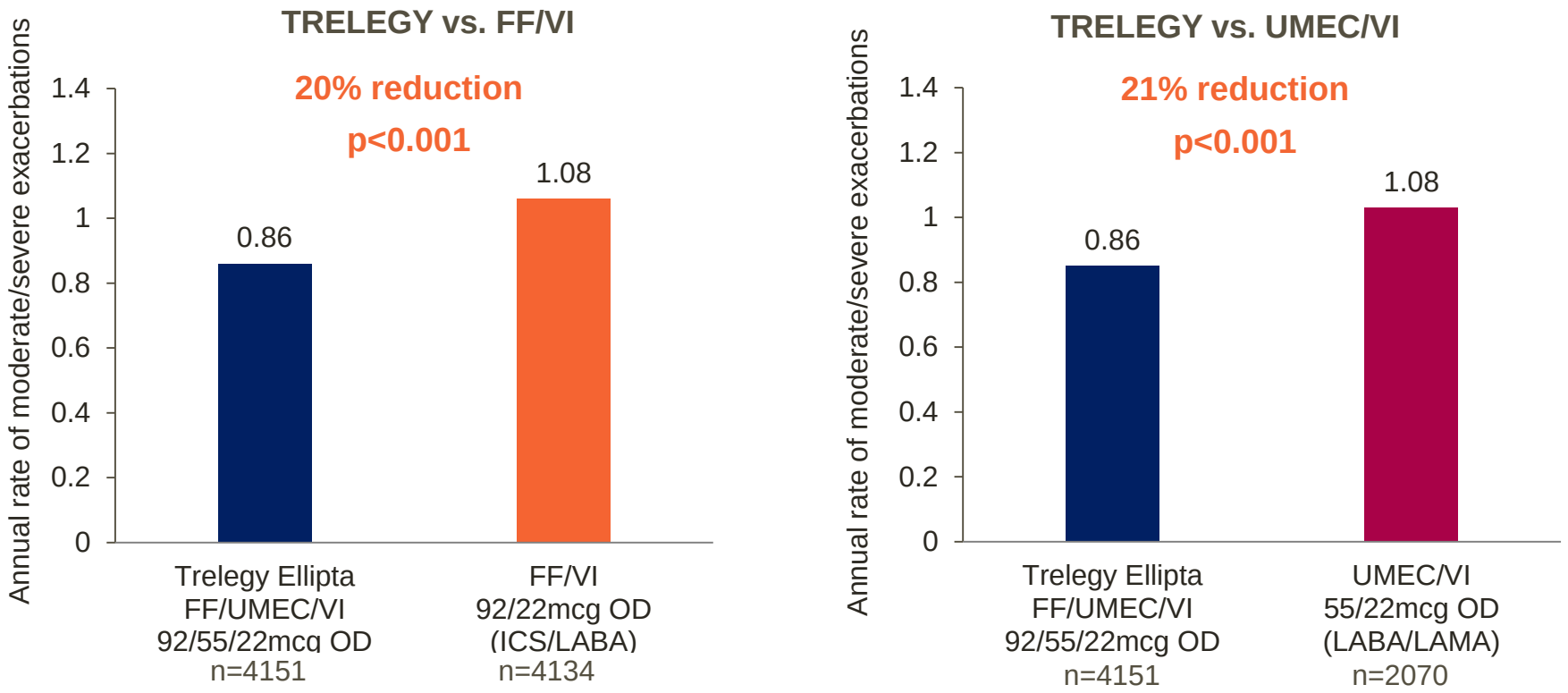
IMPACT study: reduction in annual rate of moderate/severe exacerbations with FF/UMEC/VI vs ICS/LABA and vs LAMA/LABA





Adapted from: Lipson DA, et al. N Engl J Med. 2018 May 3;378(18):1671-1680.

Exacerbation rate reduction with Trelegy in patients with one moderate exacerbation in prior year despite maintenance treatment

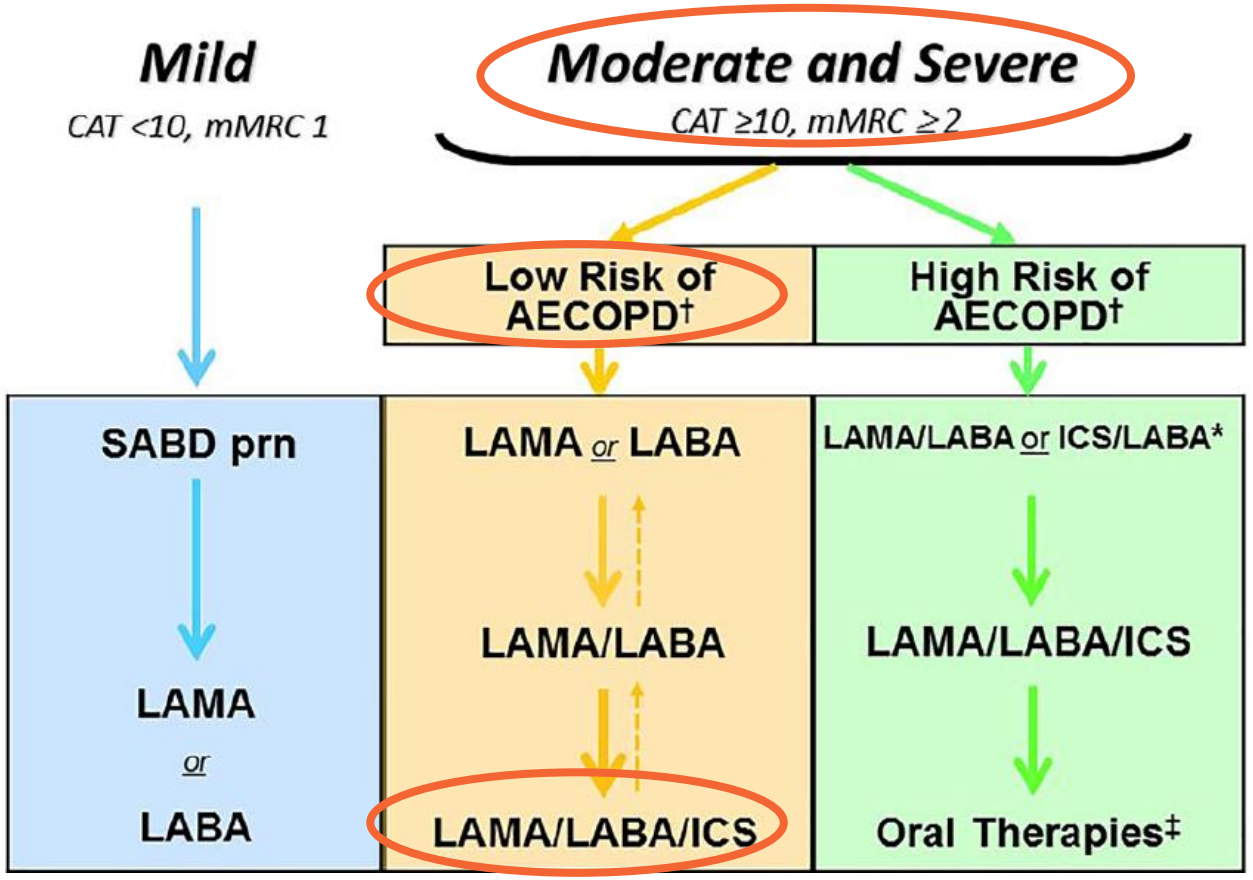


FF, fluticasone furoate; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; UMEC, umeclidinium; VI, vilanterol
*Superior exacerbation rate reduction in patients with one moderate and no severe exacerbations

Lipson DA, et al. N Engl J Med. 2018 May 3;378(18):1671-1680, supplementary.

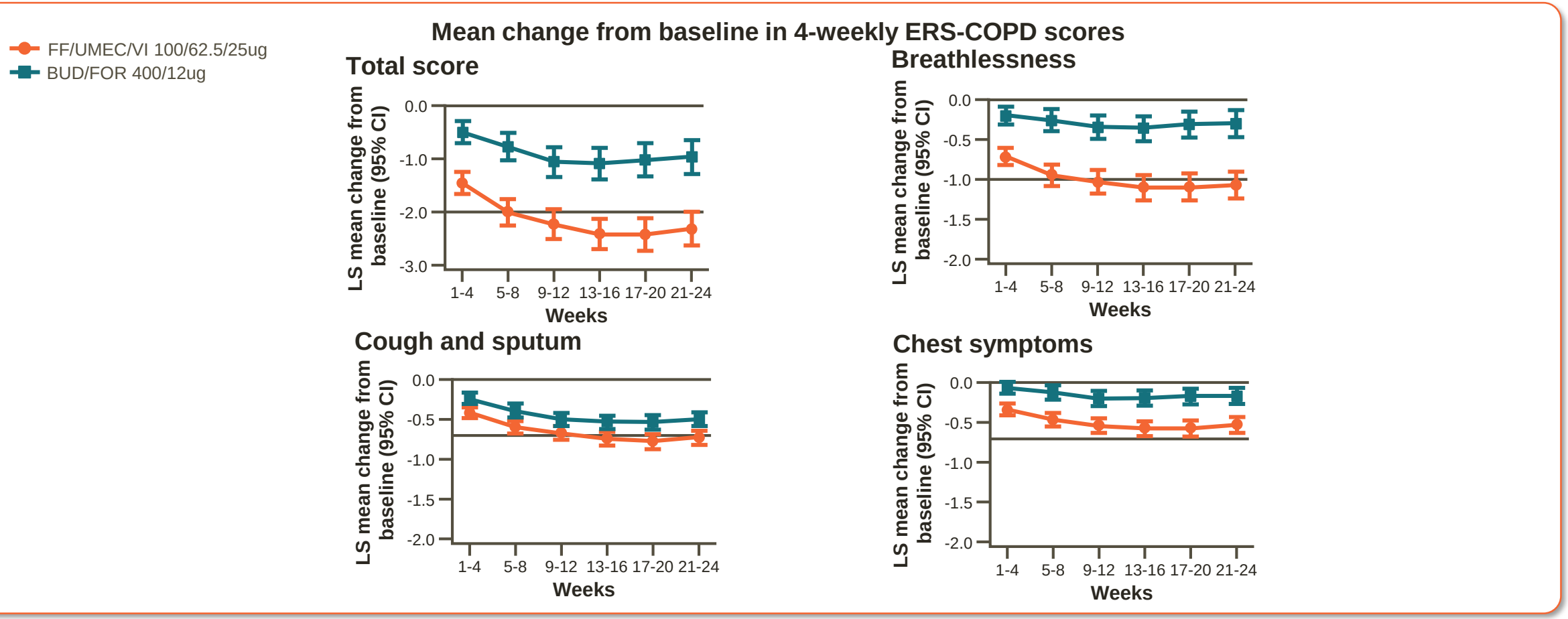
Trelegy benefits - symptoms

Canadian Thoracic Society COPD Guidelines 2019



Bourbeau et al. Canadian Journal of Respiratory, Critical Care, and Sleep Medicine
ISSN: 2474-5332 (Print) 2474-5340 (Online) Journal homepage: https://www.tandfonline.com/loi/ucts20.

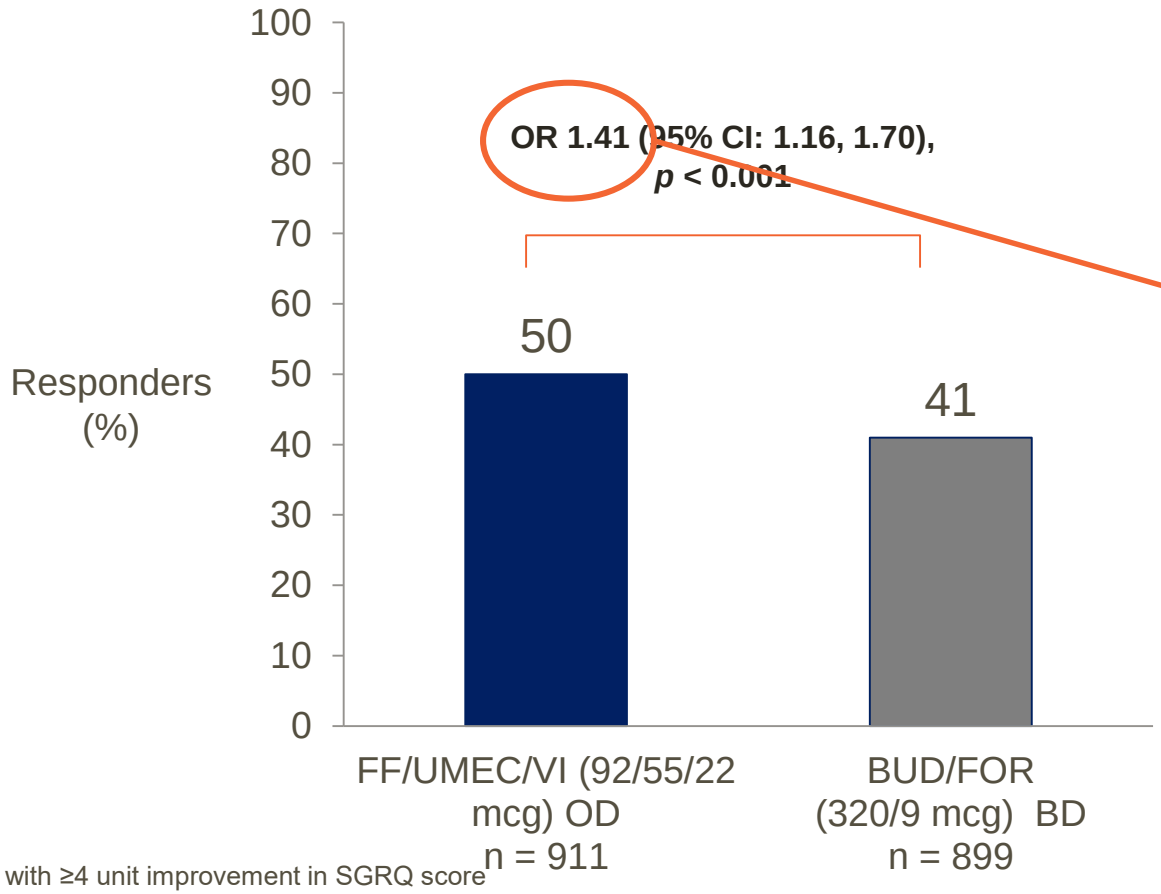
FULFIL study: Change in E-RS daily symptoms: domain scores



Treatment differences were statistically significant for each 4-week interval (*P*<0.05)
E-RS:COPD- response defined as a ≥2 unit decrease from baseline;
ITT (intent-to-treat) population included 1,810 patients (FF/UMEC/VI, n=911; BUD/FOR, n=899);

Tabberer M, et al. Adv Ther. 2018 Jan;35(1):56-71.

FULFIL study (co-primary endpoint) : Health status (SGRQ) and responder analysis* for Trelegy Ellipta OD vs BUD/FOR Turbuhaler BD

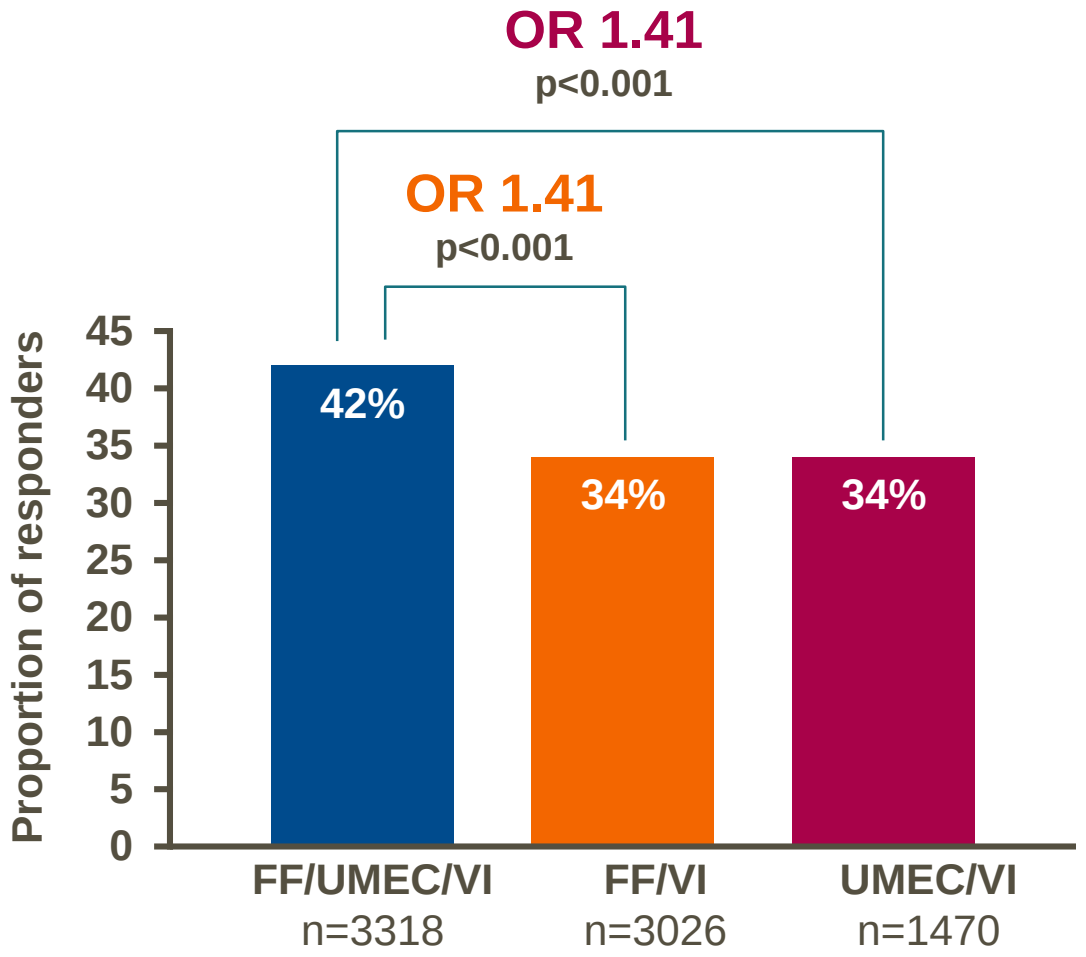


41% greater chance of a clinically significant improvement

* % of patients with ≥4 unit improvement in SGRQ score

Adapted from:Lipson DA, et al. Am J Respir Crit Care Med. 2017 Aug 15;196(4):438-446. 請參照Trelegy台灣仿單/請參照Symbicort台灣仿單

Improvement in Health Status (SGRQ score) with Trelegy vs FF/VI or UMEC/VI



Adapted from: Lipson DA, *et al.* NEJM 2018 DOI: 10.1056/NEJMoa1713901

Clinical QUESTIONS

1. **Who** are the right patients for dual-bronchodilators?
2. **Who** are the right patients for triple therapy?
3. **What** benefit will our patients get from triple therapy?
4. **Do** the benefits of triple therapy outweigh the risks?
5. **When** should we treat? Early or step up over time?

The safety profile of the three treatment arms in the IMPACT study

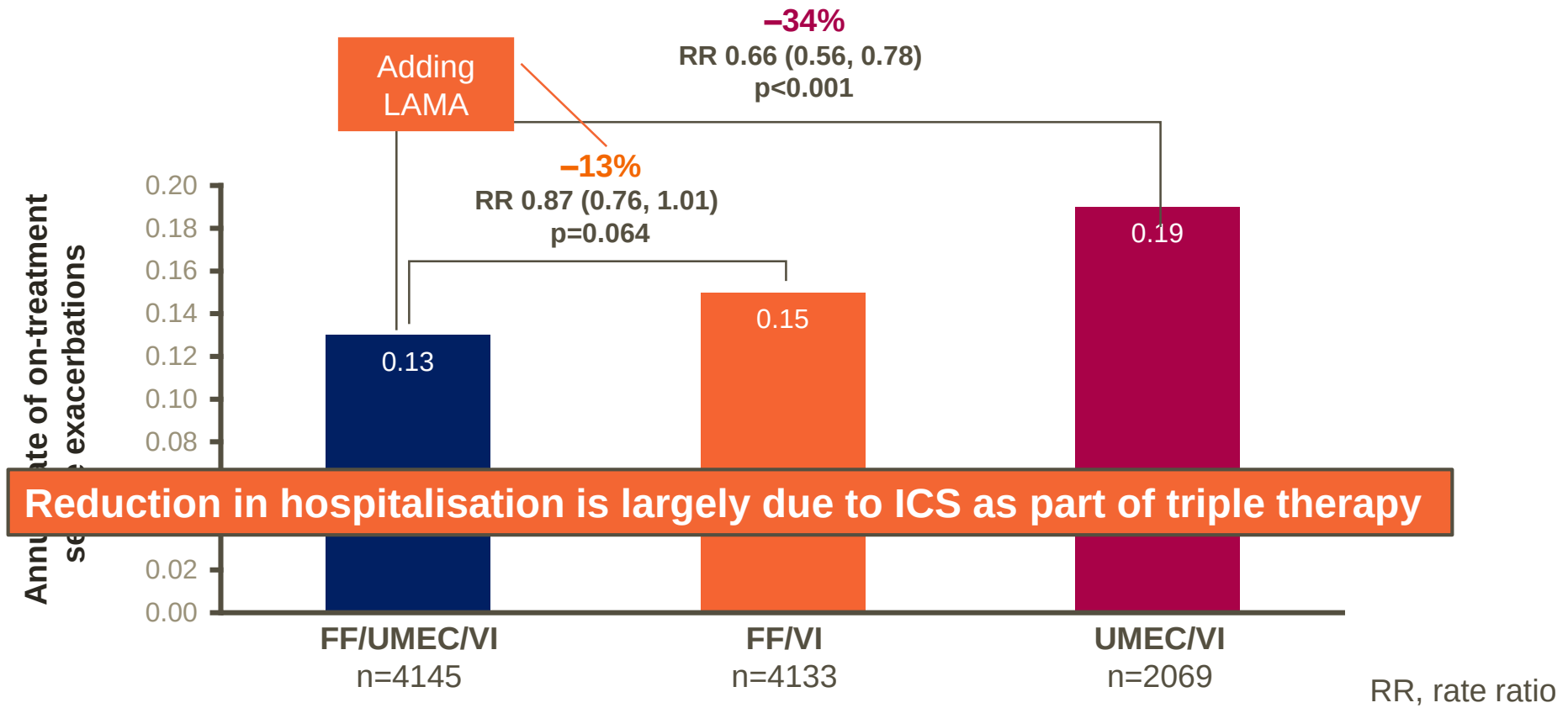
Selected safety findings	FF/UMEC/VI (n=4151)		FF/VI (n=4134)		UMEC/VI (n=2070)	
	%	Rate	%	Rate	%	Rate
Any on-treatment AEs[2]	70	2628.6	68	2593.7	69	2580.3
Any on-treatment drug-related AEs[2]	12	181.7	12	207.9	10	175.5
AEs leading to discontinuation/withdrawal[2]	6	92.1	8	128.7	9	144.3
On-treatment SAEs[2]	22	431.8	21	423.7	23	443.4
Selected AE occurring in ≥2% of patients[1]						
URTI	7	108.5	7	111.0	6	95.4
Pneumonia	7	88.6	6	86.8	4	57.7
Pneumonia	8	95.8	7	96.6	5	61.2
LRTI excluding pneumonia	5	63.0	5	69.7	5	76.0
On-treatment SAEs in ≥1% of patient[2]						
COPD worsening	11	149.1	11	164.5	13	198.4
Pneumonia	4	53.3	4	47.7	3	32.4

- 3% of patients with dual bronchodilator were hospitalised with pneumonia
- An extra 1% were hospitalised with pneumonia due to ICS

FF - fluticasone furoate, UMEC – umeclidinium, VI – vilanterol

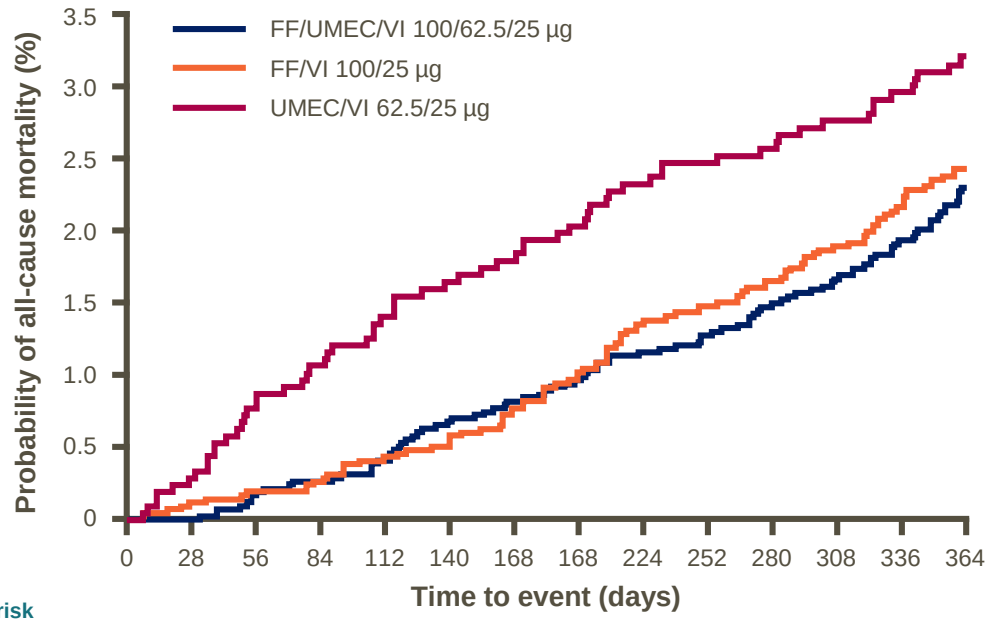
Lipson DA, et al. N Engl J Med. 2018 May 3;378(18):1671-1680. and Supplement

IMPACT study: rate of exacerbations leading to hospitalisation with FF/UMEC/VI vs LAMA/LABA



Adpated from:Lipson DA, et al. N Engl J Med. 2018 May 3;378(18):1671-1680.

Post hoc analysis on and off-treatment all-cause mortality (99.6% of ITT study population)



N at risk														
FF/UMEC/VI	4,151	4,150	4,142	4,137	4,131	4,119	4,113	4,107	4,097	4,092	4,082	4,073	4,062	3,919
FF/VI	4,134	4,129	4,123	4,118	4,111	4,106	4,095	4,082	4,065	4,060	4,050	4,040	4,027	3,848
UMEC/VI	2,070	2,063	2,052	2,045	2,037	2,030	2,027	2,021	2,013	2,008	2,004	1,999	1,995	1,914

Risk reduction (RR)

FF/UMEC/VI vs UMEC/VI

28%

(95% CI: 1, 47); *p* = 0.042

% Mortality
2.36 (n = 98)
2.64 (n = 109)
3.19 (n = 66)

Collection of additional vital status data resulted in available data for an additional 27 off-treatment deaths (providing data for 99.6% of the study population [42 censored patients]), which are included in the ACM analyses presented here.

Lipson DA, et al. ATS 2019. Poster 221 (A7344).

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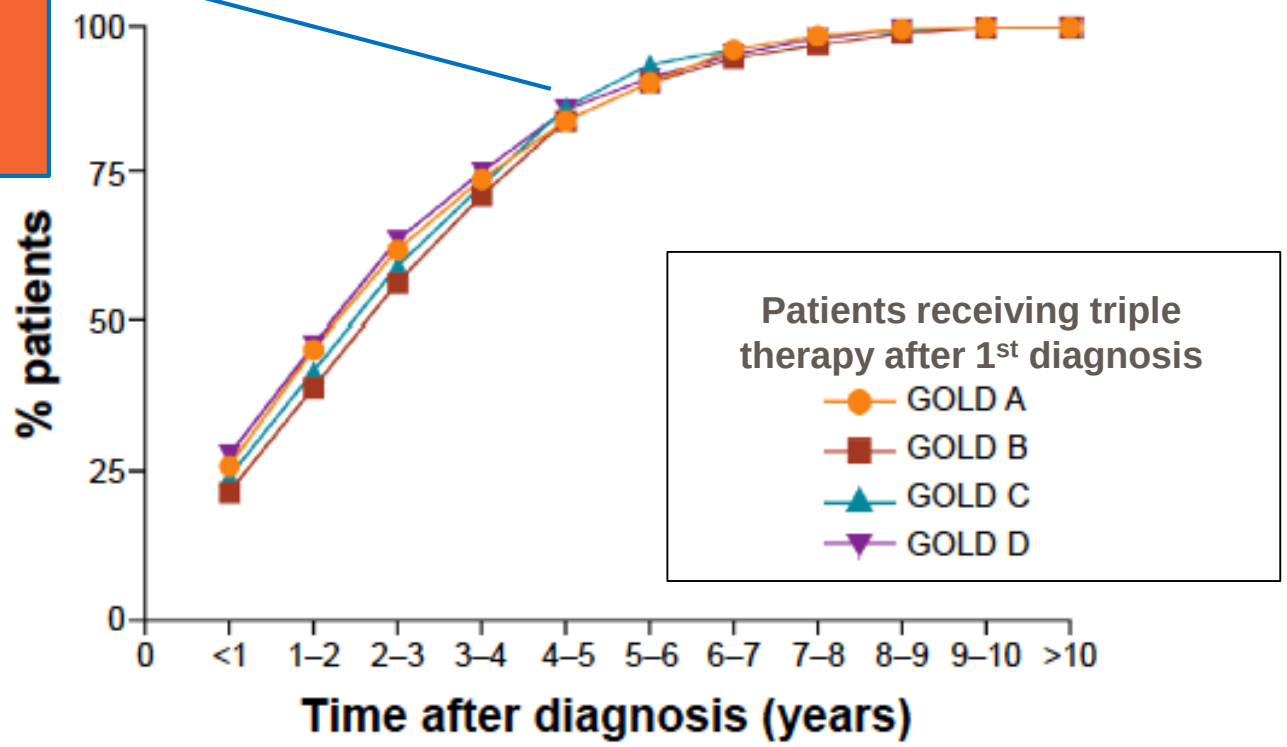
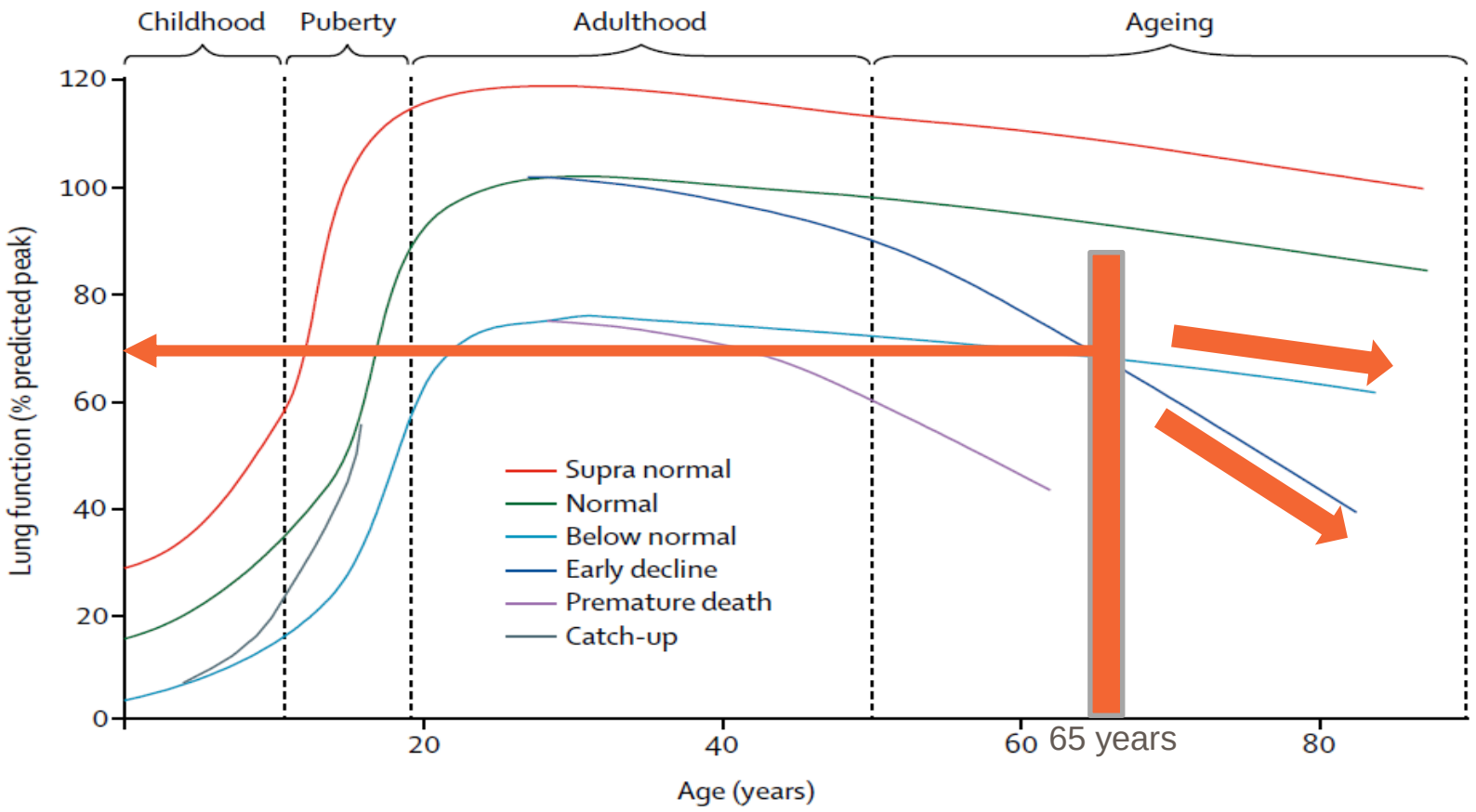
Time course from first diagnosis to prescription of triple therapy in clinical practice (UK database study)

Most patients take other treatments for several years before receiving triple therapy



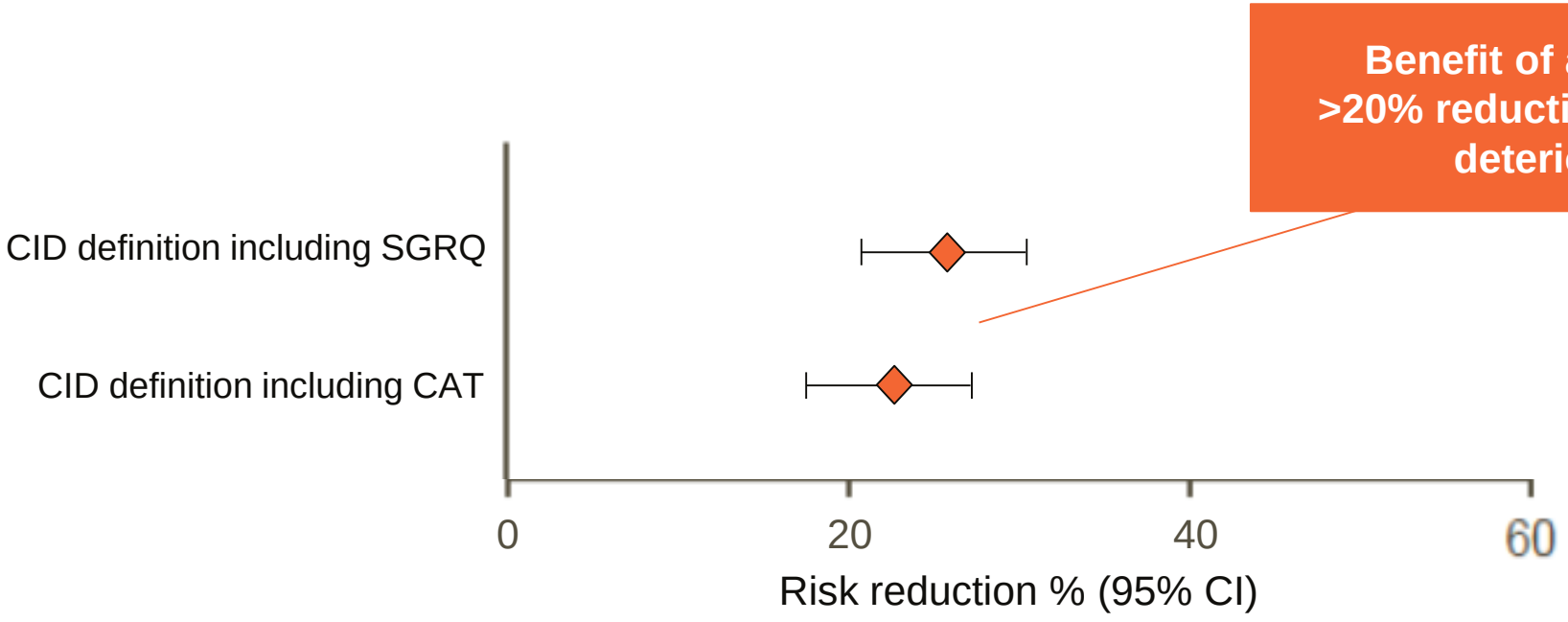
Brusselle G, et al. Int J Chron Obstruct Pulmon Dis. 2015 Oct 15;10:2207-17.

Lung function trajectories in health and disease



Agusti A,et al. Lancet Respir Med. 2019 Apr;7(4):358-364.

Reduction in risk of CID after 6 months (FF/UMEC/VI vs UMEC/VI)



Adapted from: Han et al.ATS 2019 abstract A2438(poster no.204)

Summary

Clear benefit of once daily Trelegy over

- Twice daily ICS/LABA
- Once daily ICS/LABA
- Once daily dual bronchodilator

Benefits seen in

- Lung function
- Exacerbations
- Symptoms
- Health status
- Hospitalization
- Mortality

The benefits of Trelegy outweigh the risk of pneumonia

Strong arguments to support earlier use of Trelegy