

COPD: State of the Art

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By the end of this presentation ...

- Appreciate the current burden and **realities of COPD**
- Understand recent new evidence, and updates to recommendations for the **optimal management of COPD**, with view to reducing symptom burden and preventing AECOPD
- Utilize effective interventions and strategies, including **pharmacologic, non-pharmacologic and healthcare system practices**, to improve the care and outcomes for patients suffering from COPD



Conflict of Interest Disclosure

Consultancy

Alberta Lung Association, AstraZeneca, Boehringer-Ingelheim, Canadian Foundation for Healthcare Improvement, Chinese Committee of Health and Family Planning, GlaxoSmithKline, Health Canada, Lung Association of Saskatchewan, Mylan, Novartis, Saskatchewan Ministry of Health, Saskatchewan Health Authority, Yukon Health and Social Services

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Employee

University of Saskatchewan



Realities of COPD

- **COPD affects >200 million people in the world**
 - 65-100 million of whom have moderate or severe disease¹
- COPD is the **3rd leading cause of death** globally^{2,3}
 - **3 million deaths annually** (31% more than TB + HIV combined)
- **Under-diagnosis and misdiagnosis of COPD is common**⁶
 - much higher than for hypertension or hypercholesterolemia
- **Prevalence, burden, and deaths from COPD are projected to increase over the coming decades**^{4,5}
 - with aging of the world's population, more people will express the long-term effects of exposure to COPD risk factors

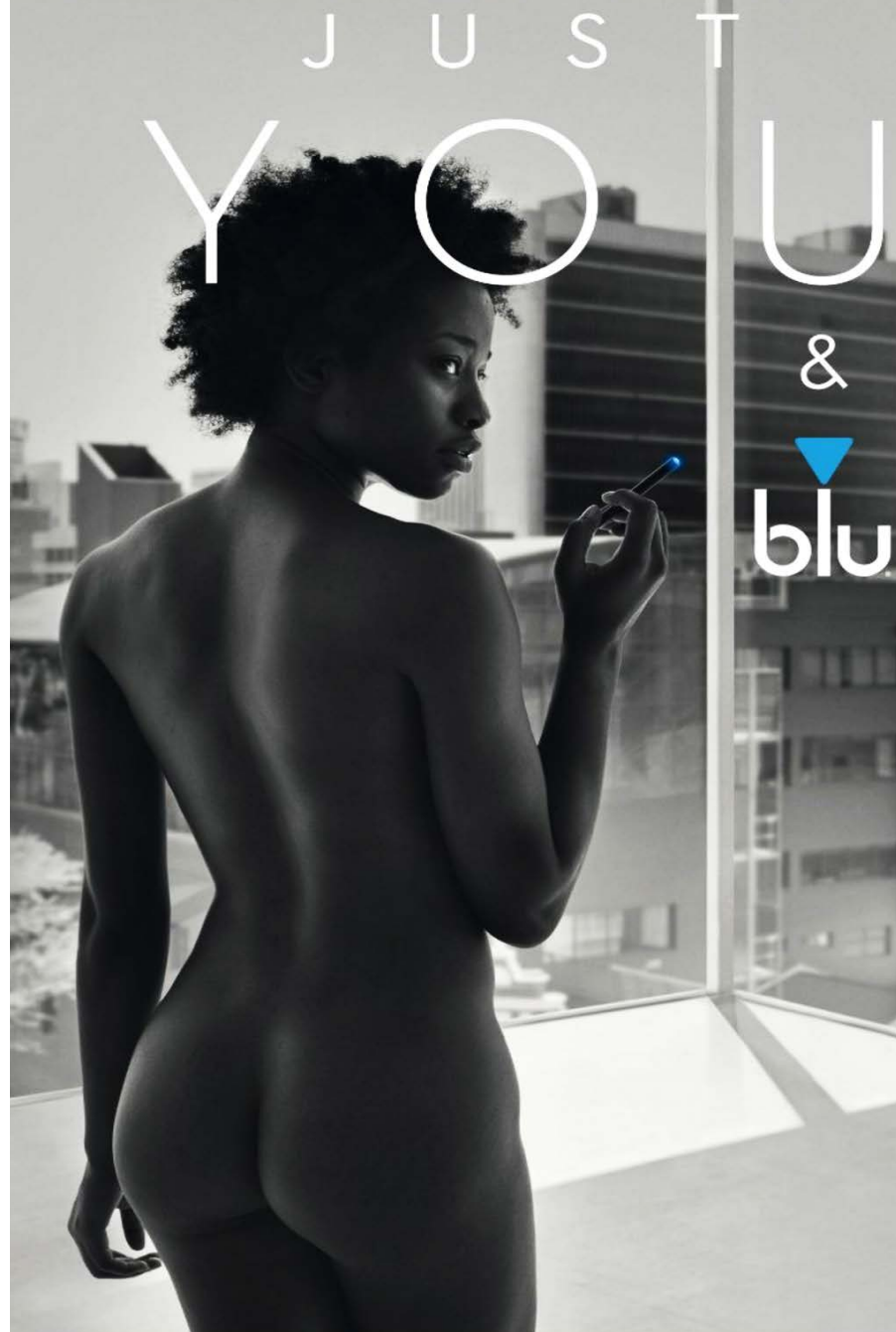
¹WHO. <http://www.who.int/gard/1-3.GARD-06-07-K1.pdf>.

²Burney PG, et al. *Eur Respir J* 2015; 45:1239-47. ³Global Burden of Disease Study. *Lancet* 2017; 390:1151-1210. ⁴Mathers CD, et al. *PLoS Med* 2006; 3:e442.

⁵WHO. http://www.who.int/healthinfo/global_burden_Disease/projections/en/. ⁶Talamo C, et al. *Chest* 2007; 131:60-67.



1969



'blu' unveils a new global brand campaign – celebrating freedom and individuality

2016



‘More’ Realities of COPD ...

- **COPD is the most common chronic medical condition leading to hospitalization in adults¹**
 - most frequent cause of ‘*ambulatory care preventable*’ hospital admission ²
- **25% mortality in AECOPD pts admitted with hypercapnic respiratory failure, with overall hospital mortality 7-11% ³**
 - 21% 1-yr / 55% 5-yr mortality for survivors ⁴
 - pts with 1st admission for AECOPD, 34% had not been previously diagnosed ⁵
- Recognition that the impact and **consequences of AECOPD are very similar to ACS** ^{6,7}

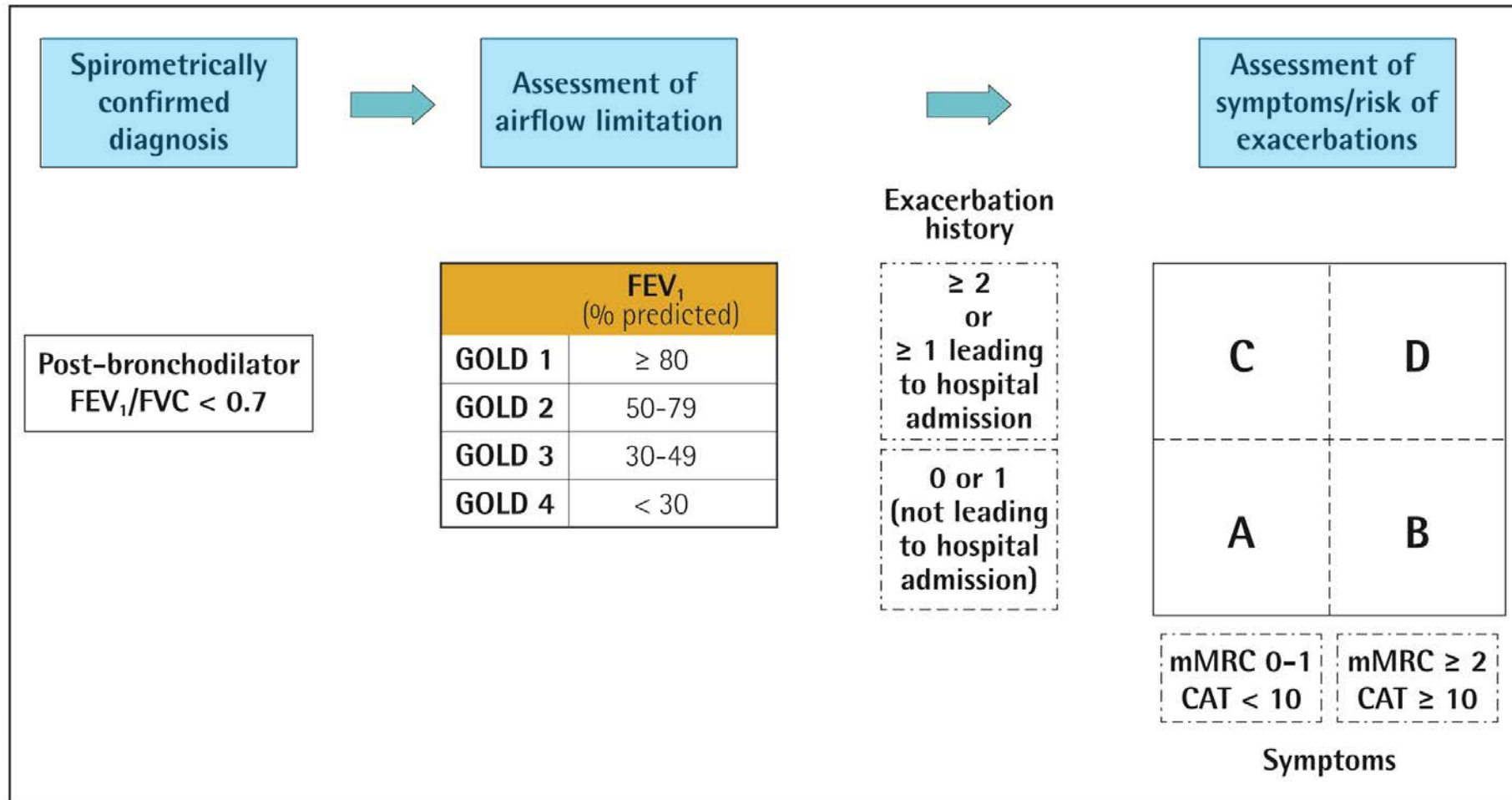
Global Initiative for Chronic Obstructive Lung Disease



**GLOBAL STRATEGY FOR THE DIAGNOSIS,
MANAGEMENT, AND PREVENTION OF
CHRONIC OBSTRUCTIVE PULMONARY DISEASE**
2019 REPORT



“Refined” ABCD Assessment Tool





Treatment of Stable COPD

INITIAL PHARMACOLOGICAL TREATMENT

≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization

Group C

LAMA

Group D

LAMA or
LAMA + LABA* or
ICS + LABA**

*Consider if highly symptomatic (e.g. CAT > 20)

**Consider if eos ≥ 300

0 or 1 moderate exacerbations (not leading to hospital admission)

Group A

A Bronchodilator

Group B

A Long Acting Bronchodilator
(LABA or LAMA)

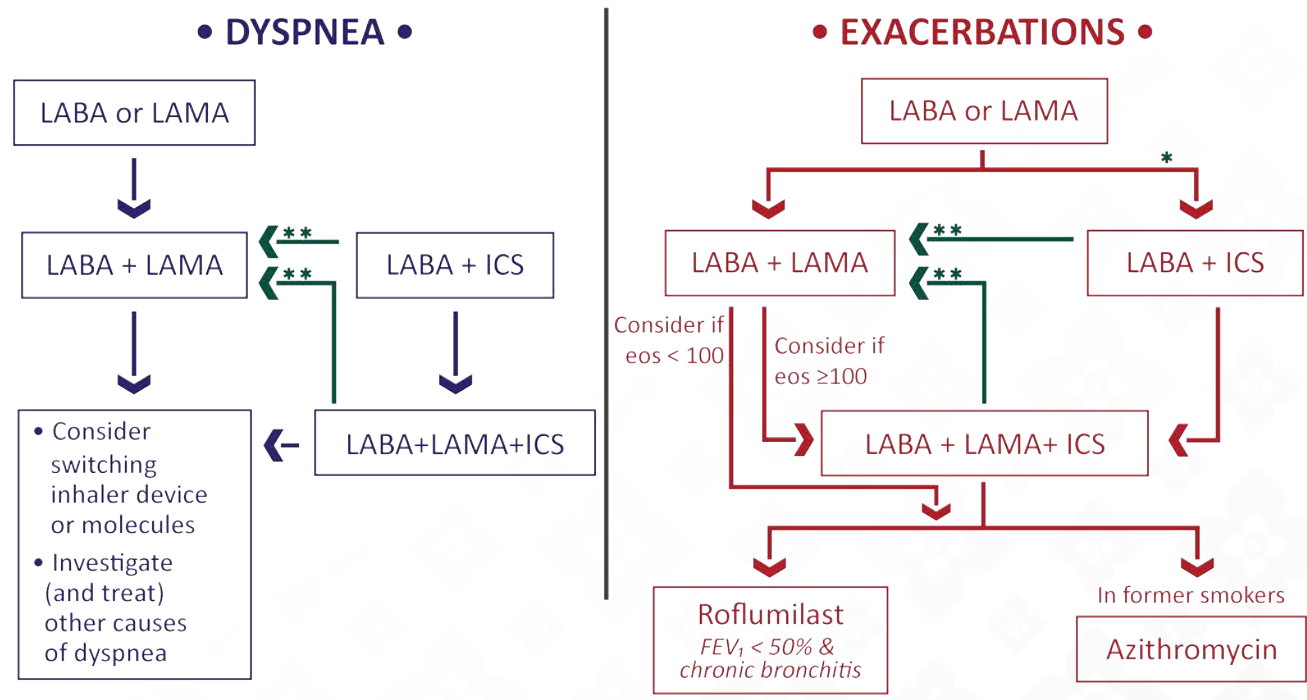
mMRC 0-1 CAT < 10

mMRC ≥ 2 CAT ≥ 10



FOLLOW-UP PHARMACOLOGICAL TREATMENT

- IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.
- IF NOT:
 - ✓ 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 ABCD assessment at diagnosis

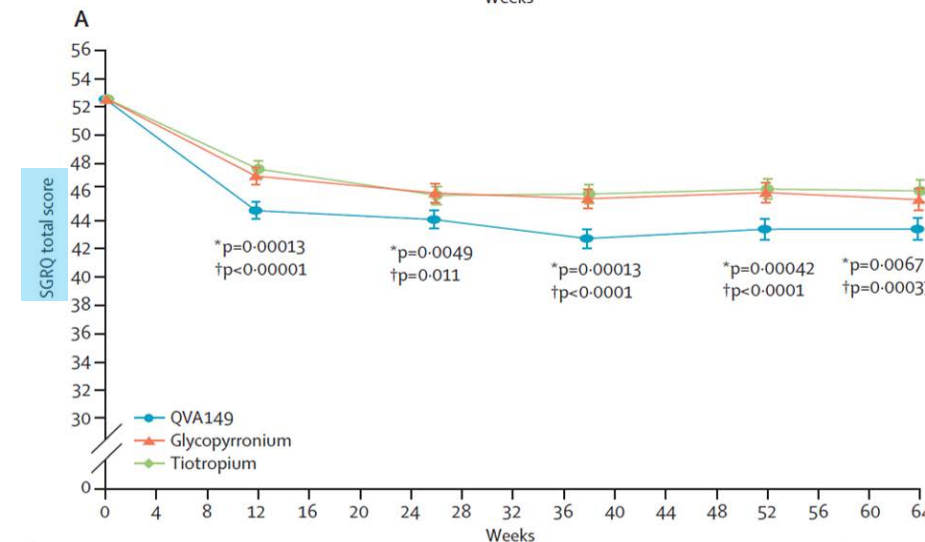
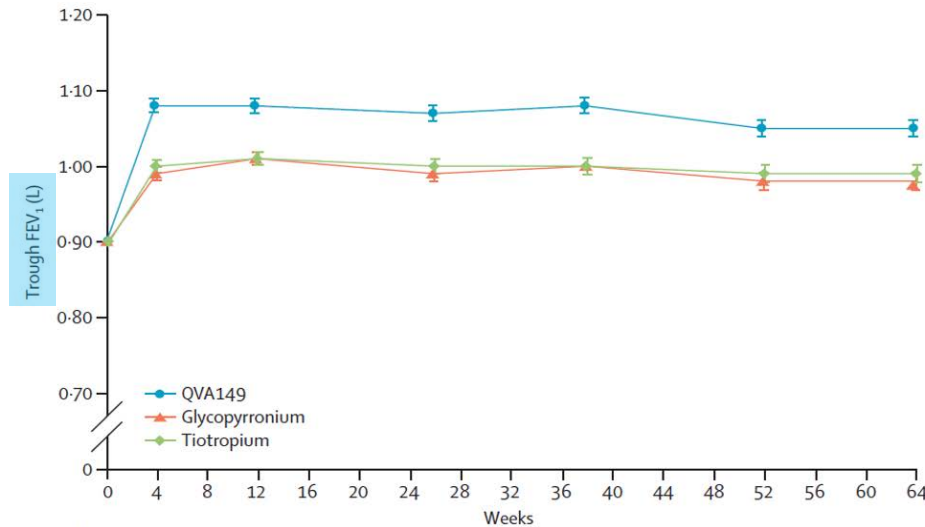


eos = blood eosinophil count (cells/ μ L)
 * Consider if eos \geq 300 or eos \geq 100 AND \geq 2 moderate exacerbations / 1 hospitalization
 ** Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS

Follow-up Pharmacologic Treatment



Combination Long-Acting Bronchodilators



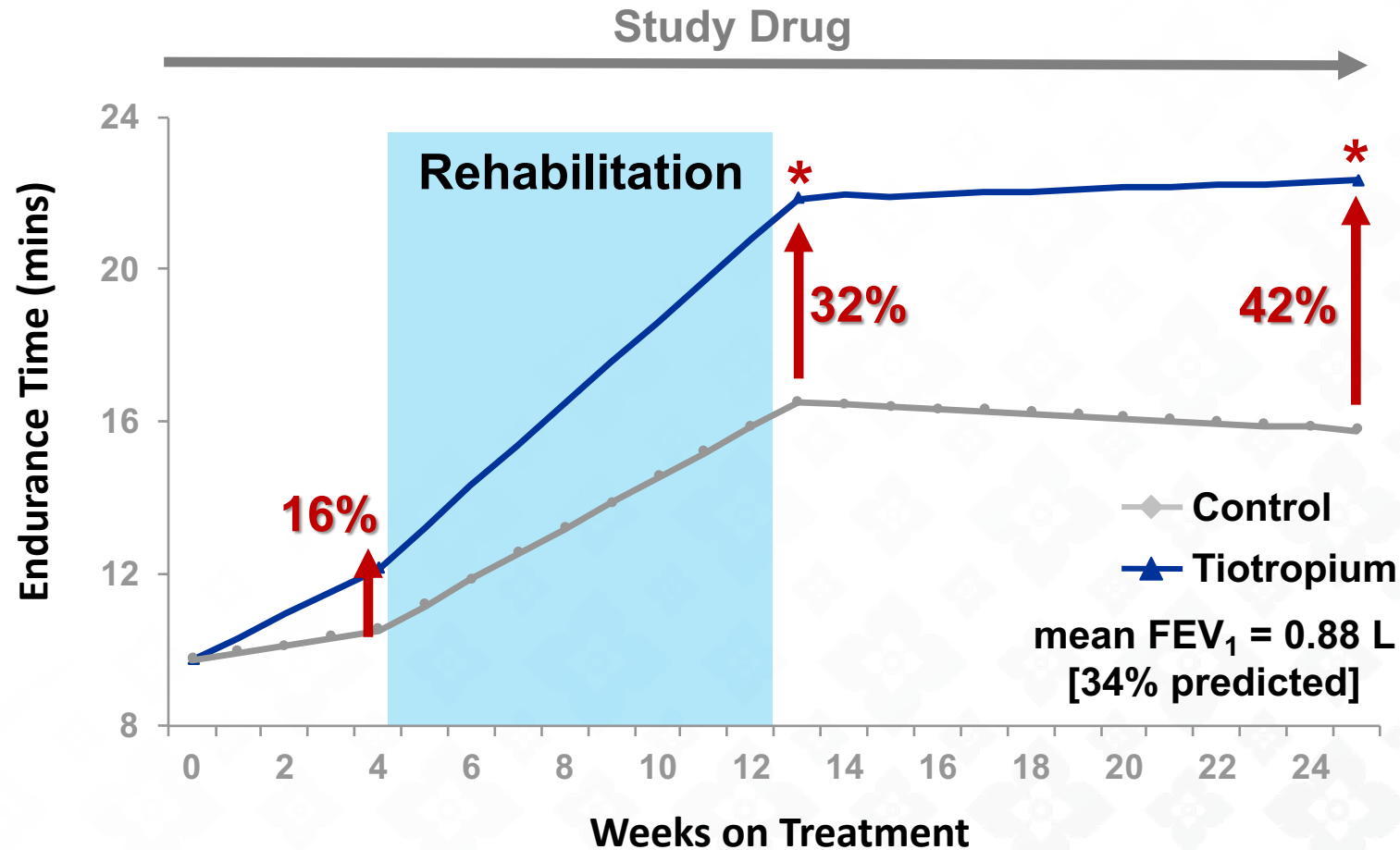
n=2224
subjects;

FEV₁ < 50%
predicted;

mean FEV₁ =
1.04 L
[37%
predicted]



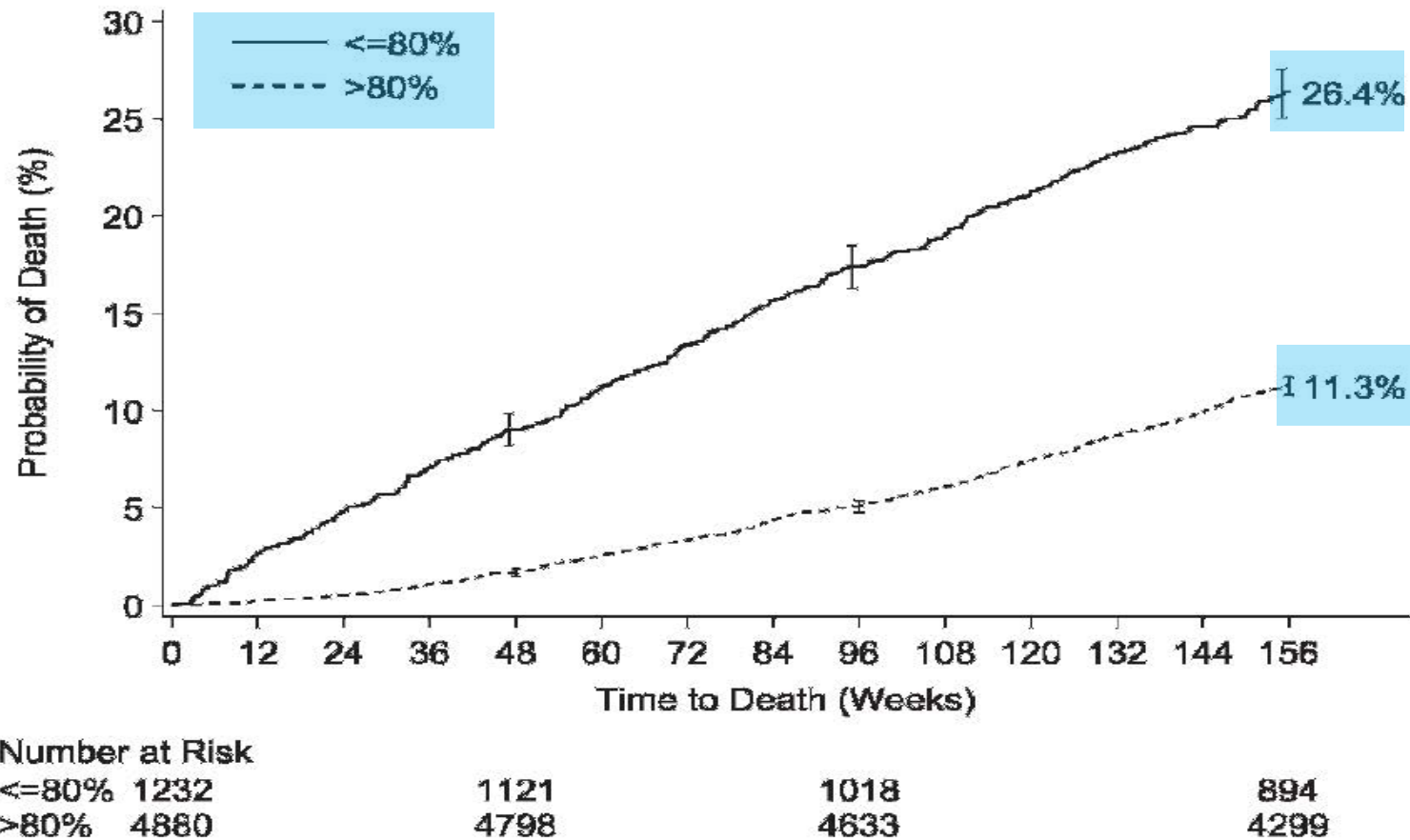
Bronchodilation and Pulmonary Rehabilitation



* = p<0.05



Adherence – Effect on Outcomes



Kaplan-Meier plot of survival in subjects adherent, and not adherent to therapy (n=6112)

CTS position statement: Pharmacotherapy in patients with COPD—An update

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ABSTRACT

RATIONALE: Since the last published Canadian Thoracic Society (CTS) COPD guideline in 2007 and the 2008 update – highlights for primary care, many new clinical trials have challenged COPD treatment practices. The current Canadian position statement provides the reader with an update on pharmacotherapy of patients with COPD as reviewed by the CTS.

OBJECTIVES: The objectives of this position statement are: 1) to summarize the literature on topics relevant to the pharmacological therapy of patients with stable COPD; and 2) to provide clinical guidance with evidence-based recommendations and expert-informed key messages for the pharmacological therapy for patients with stable COPD.

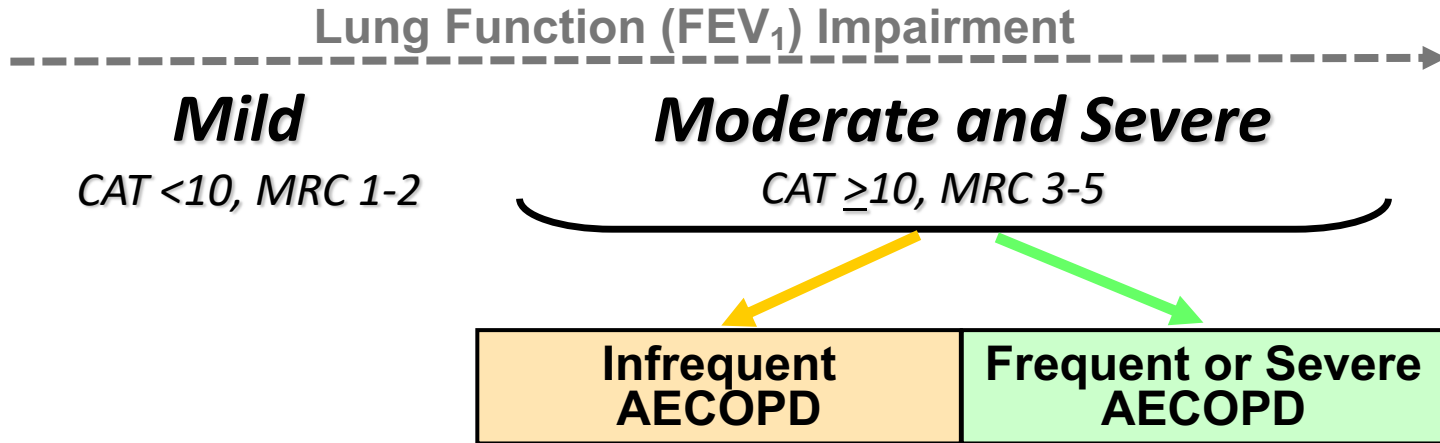
METHODS: The authors systematically reviewed the relevant literature focusing on randomized controlled trials and when available, systematic reviews of randomized controlled trials. The proposed key messages, based on scientific evidence and expert-informed opinion, were agreed upon by a majority consensus.

MAIN RESULTS: There is typically a significant delay in seeking medical care by patients with dyspnea, often waiting until symptoms affect the performance of activities of daily living. The diagnosis of COPD requires spirometry to confirm the presence of airflow obstruction in any patient presenting with symptoms and/or risk factors of COPD. An effective management plan for individuals with COPD should include: smoking cessation, vaccination and education. A number of non-pharmacological treatments are available for COPD patients with symptoms to improve outcomes such as self-management with coaching from a health care

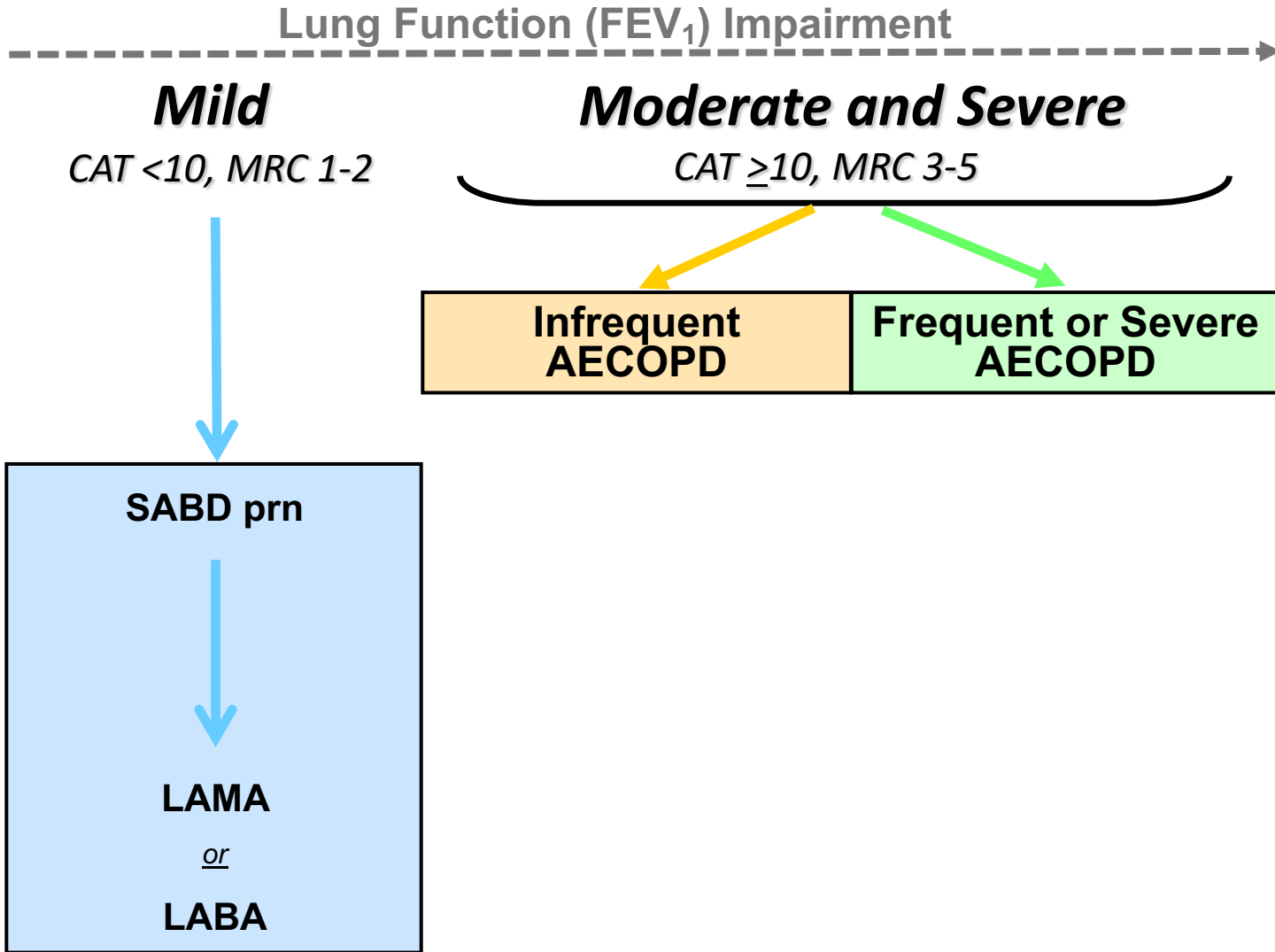
KEYWORDS

Position statement; COPD;
ACO; ACOS;
pharmacotherapy

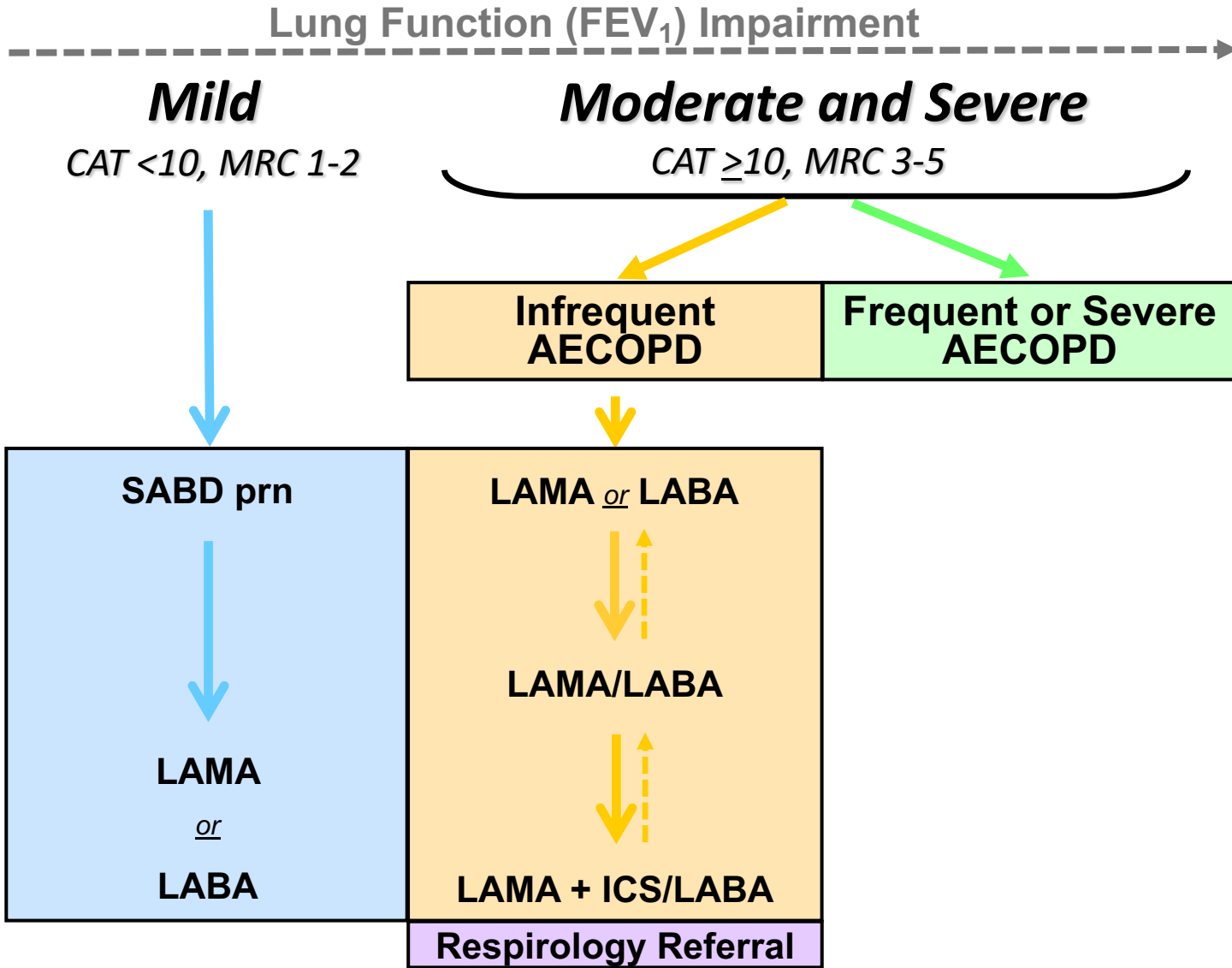
COPD Pharmacotherapy



COPD Pharmacotherapy



COPD Pharmacotherapy





What's the Big Deal with AECOPD?

- **AECOPD are a 'gateway' to:** ^{1,2}
 - accelerated **decreases in lung function**
 - **worsened quality of life**
 - the next, and more frequent, **AECOPD**
 - increased healthcare utilization, including **emergency department visits** and **hospitalizations**
 - increased **mortality**
- **Exacerbations are a trigger ('opportunity')** for patients to come to the attention of the healthcare system and for clinicians to consider the diagnosis of COPD or to optimize management



Hospital Costs Canada 2016-2017

Top 5 conditions Total hospital cost



\$753.3M

1

Chronic obstructive pulmonary disease



\$575.2M

2

Heart failure without coronary angiogram



\$505.8M

3

Viral/unspecified pneumonia



\$486.4M

4

Unilateral knee replacement



\$404.0M

5

Dementia

Prevention of Acute Exacerbations of COPD

American College of Chest Physicians and Canadian Thoracic Society Guideline

Gerard J. Criner, MD, FCCP; Jean Bourbeau, MD, FCCP; Rebecca L. Diekemper, MPH; Daniel R. Ouellette, MD, FCCP; Donna Goodridge, RN, PhD; Paul Hernandez, MDCM; Kristen Curren, MA; Meyer S. Balter, MD, FCCP; Mohit Bhutani, MD, FCCP; Pat G. Camp, PhD, PT; Bartolome R. Celli, MD, FCCP; Gail Dechman, PhD, PT; Mark T. Dransfield, MD; Stanley B. Fiel, MD, FCCP; Marilyn G. Foreman, MD, FCCP; Nicola A. Hanania, MD, FCCP; Belinda K. Ireland, MD; Nathaniel Marchetti, DO, FCCP; Darcy D. Marciniuk, MD, FCCP; Richard A. Mularski, MD, MSHS, MCR, FCCP; Joseph Ornelas, MS; Jeremy D. Road, MD; and Michael K. Stickland, PhD



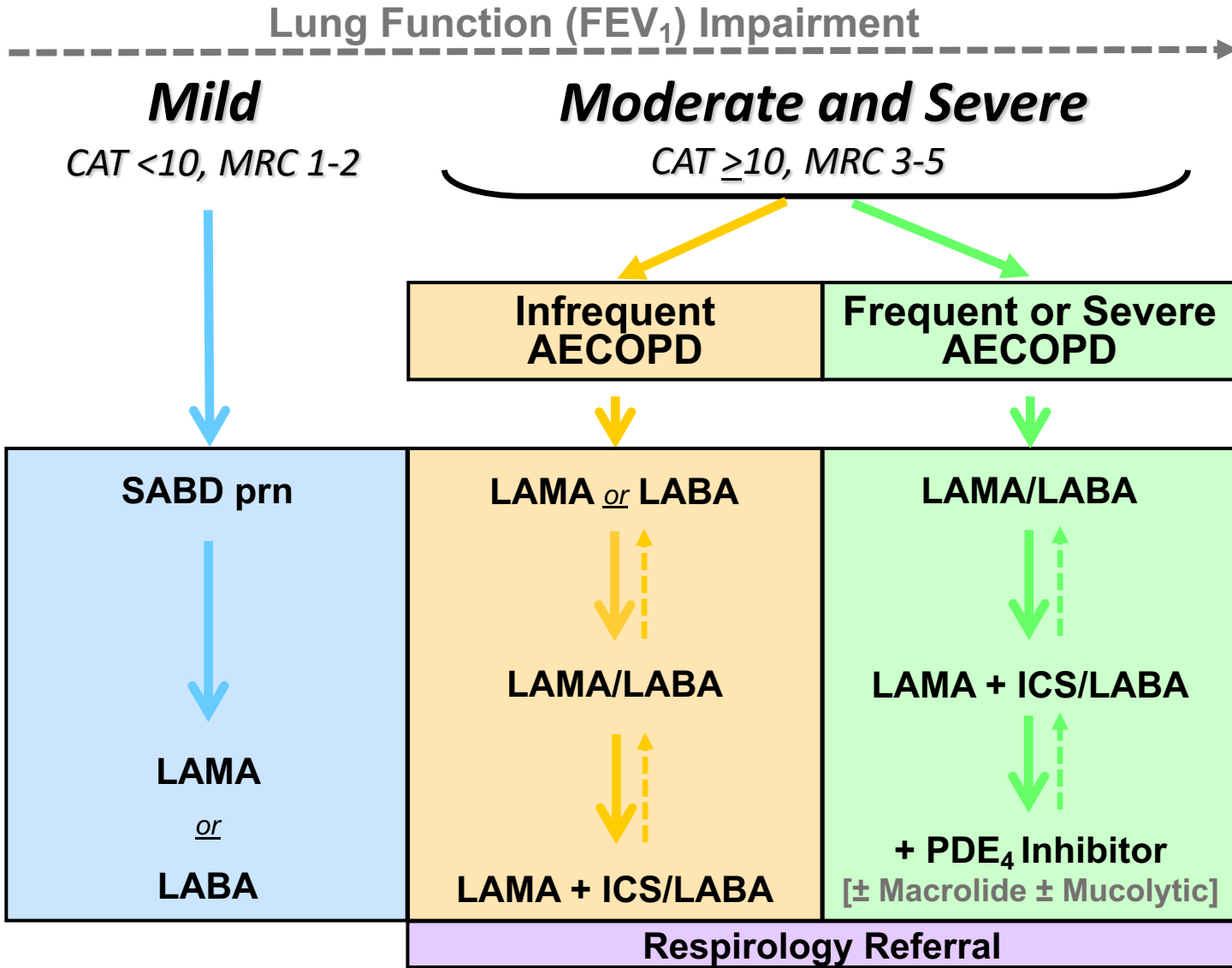
BACKGROUND: COPD is a major cause of morbidity and mortality in the United States as well as throughout the rest of the world. An exacerbation of COPD (periodic escalations of symptoms of cough, dyspnea, and sputum production) is a major contributor to worsening lung function, impairment in quality of life, need for urgent care or hospitalization, and cost of care in COPD. Research conducted over the past decade has contributed much to our current understanding of the pathogenesis and treatment of COPD. Additionally, an evolving literature has accumulated about the prevention of acute exacerbations.

METHODS: In recognition of the importance of preventing exacerbations in patients with COPD, the American College of Chest Physicians (CHEST) and Canadian Thoracic Society (CTS) joint evidence-based guideline (AECOPD Guideline) was developed to provide a practical, clinically useful document to describe the current state of knowledge regarding the prevention of acute exacerbations according to major categories of prevention therapies. Three key clinical questions developed using the PICO (population, intervention, comparator, and outcome) format addressed the prevention of acute exacerbations of COPD: nonpharmacologic therapies, inhaled therapies, and oral therapies. We used recognized document evaluation tools to assess and choose the most appropriate studies and to extract meaningful data and grade the level of evidence to support the recommendations in each PICO question in a balanced and unbiased fashion.

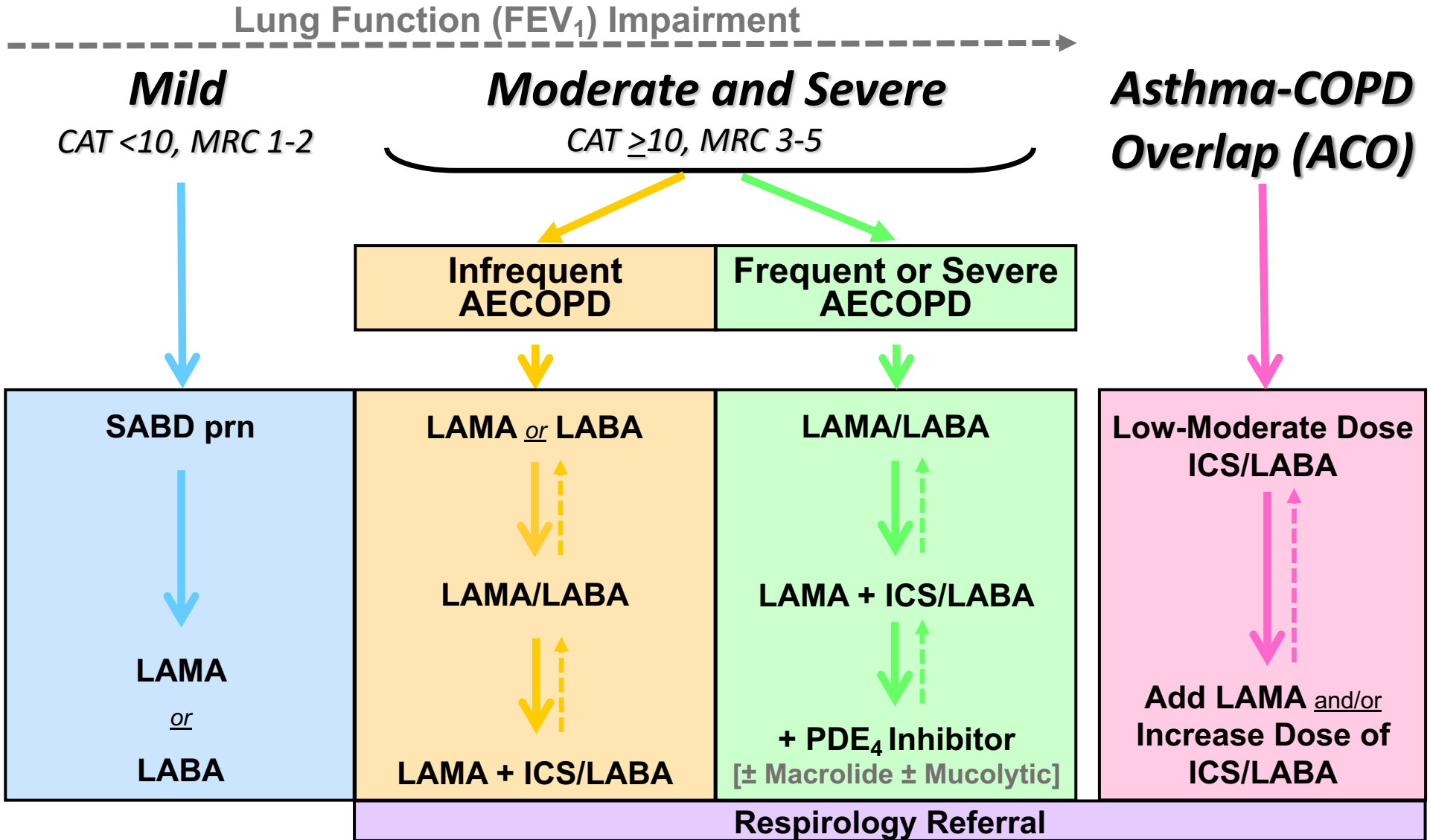
RESULTS: The AECOPD Guideline is unique not only for its topic, the prevention of acute exacerbations of COPD, but also for the first-in-kind partnership between two of the largest thoracic societies in North America. The CHEST Guidelines Oversight Committee in partnership with the CTS COPD Clinical Assembly launched this project with the objective that a systematic review and critical evaluation of the published literature by clinical experts and researchers in the field of COPD would lead to a series of recommendations to assist clinicians in their management of the patient with COPD.

CONCLUSIONS: This guideline is unique because it provides an up-to-date, rigorous, evidence-based analysis of current randomized controlled trial data regarding the prevention of COPD exacerbations. CHEST 2015; 147(4):894-942

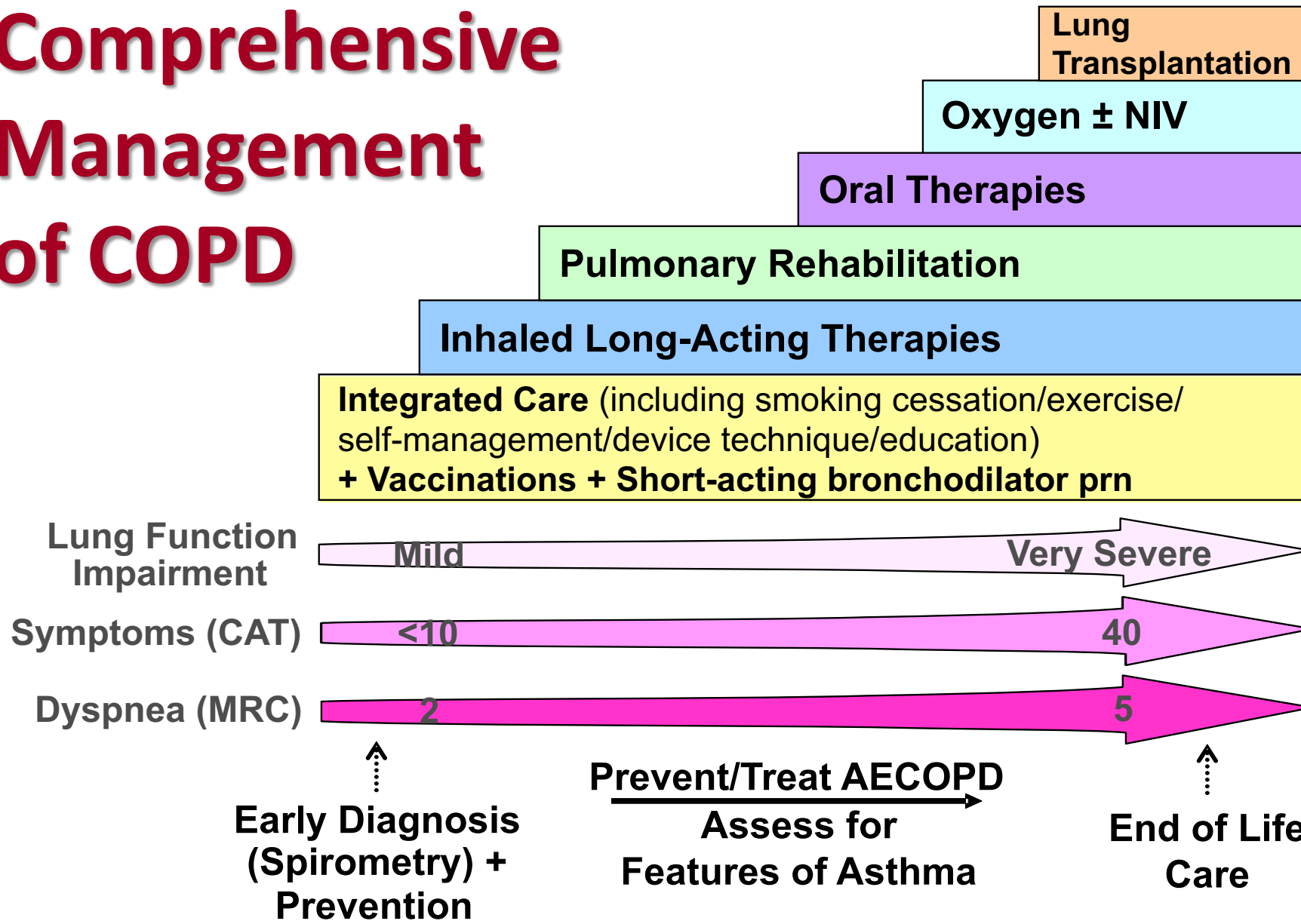
COPD Pharmacotherapy



COPD Pharmacotherapy



Comprehensive Management of COPD



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

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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.,
C. Elaine Jones, Ph.D., Sally Kilbride, M.Sc., Peter Lange, M.D.,
David A. Lomas, M.D., Ph.D., Fernando J. Martinez, M.D., Dave Singh, M.D.,
Maggie Tabberer, M.Sc., Robert A. Wise, M.D., and Steven J. Pascoe, M.B., B.S.,
for the IMPACT Investigators

ABSTRACT

BACKGROUND

The benefits of triple therapy for chronic obstructive pulmonary disease (COPD) with an inhaled glucocorticoid, a long-acting muscarinic antagonist (LAMA), and a long-acting β_2 -agonist (LABA), as compared with dual therapy (either inhaled glucocorticoid–LABA or LAMA–LABA), are uncertain.

METHODS

In this randomized trial involving 10,355 patients with COPD, we compared 52 weeks of a once-daily combination of fluticasone furoate (an inhaled glucocorticoid) at a dose of 100 μg , umeclidinium (a LAMA) at a dose of 62.5 μg , and vilanterol (a LABA) at a dose of 25 μg (triple therapy) with fluticasone furoate–vilanterol (at doses of 100 μg and 25 μg , respectively) and umeclidinium–vilanterol (at doses of 62.5 μg and 25 μg , respectively). Each regimen was administered in a single Ellipta inhaler. The primary outcome was the annual rate of moderate or severe COPD exacerbations during treatment.

RESULTS

The rate of moderate or severe exacerbations in the triple-therapy group was 0.91 per year, as compared with 1.07 per year in the fluticasone furoate–vilanterol group (rate ratio with triple therapy, 0.85; 95% confidence interval [CI], 0.80 to 0.90; 15% difference; $P<0.001$) and 1.21 per year in the umeclidinium–vilanterol group (rate ratio with triple therapy, 0.75; 95% CI, 0.70 to 0.81; 25% difference; $P<0.001$). The annual rate of severe exacerbations resulting in hospitalization in the triple-therapy group was 0.13, as compared with 0.19 in the umeclidinium–vilanterol group (rate ratio, 0.66; 95% CI, 0.56 to 0.78; 34% difference; $P<0.001$). There was a higher incidence of pneumonia in the inhaled-glucocorticoid groups than in the umeclidinium–vilanterol group, and the risk of clinician-diagnosed pneumonia was significantly higher with triple therapy than with umeclidinium–vilanterol, as assessed in a time-to-first-event analysis (hazard ratio, 1.53; 95% CI, 1.22 to 1.92; $P<0.001$).

CONCLUSIONS

Triple therapy with fluticasone furoate, umeclidinium, and vilanterol resulted in a lower rate of moderate or severe COPD exacerbations than fluticasone furoate–vilanterol or umeclidinium–vilanterol in this population. Triple therapy also resulted in a lower rate of hospitalization due to COPD than umeclidinium–vilanterol. (Funded by GlaxoSmithKline; IMPACT ClinicalTrials.gov number, NCT02164513.)

From GlaxoSmithKline, Collegeville (D.A. Lipson, J.B., S.J.P.), and the Perelman School of Medicine, University of Pennsylvania (D.A. Lipson), and Lewis Katz School of Medicine at Temple University (G.J.C.), Philadelphia — all in Pennsylvania; GlaxoSmithKline, Research Triangle Park, NC (F.B., C.E.J.); GlaxoSmithKline, Stockley Park West, Uxbridge (N.B., N.C.D., S.K., M.T.), the Department of Respiratory Medicine, Royal Devon and Exeter Hospital, Exeter (D.M.G.H.), UCL Respiratory, University College London, London (D.A. Lomas), and the Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, Manchester Academic Health Science Centre, University of Manchester, Manchester University NHS Foundation Trust, Manchester (D.S.) — all in the United Kingdom; the Division of Pulmonary, Allergy, and Critical Care Medicine, Lung Health Center, University of Alabama at Birmingham, Birmingham (M.T.D.); the Division of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor (M.K.H.); the Department of Public Health, University of Copenhagen, Copenhagen (P.L.), and the Medical Department, Pulmonary Section, Herlev–Gentofte Hospital, Herlev (P.L.) — both in Denmark; New York–Presbyterian Hospital/Weill Cornell Medical Center, New York (F.J.M.); and the Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore (R.A.W.). Address reprint requests to Dr. Lipson at GlaxoSmithKline, 1250 S. Collegeville Rd., Collegeville, PA 19426, or at david.a.lipson@gsk.com.

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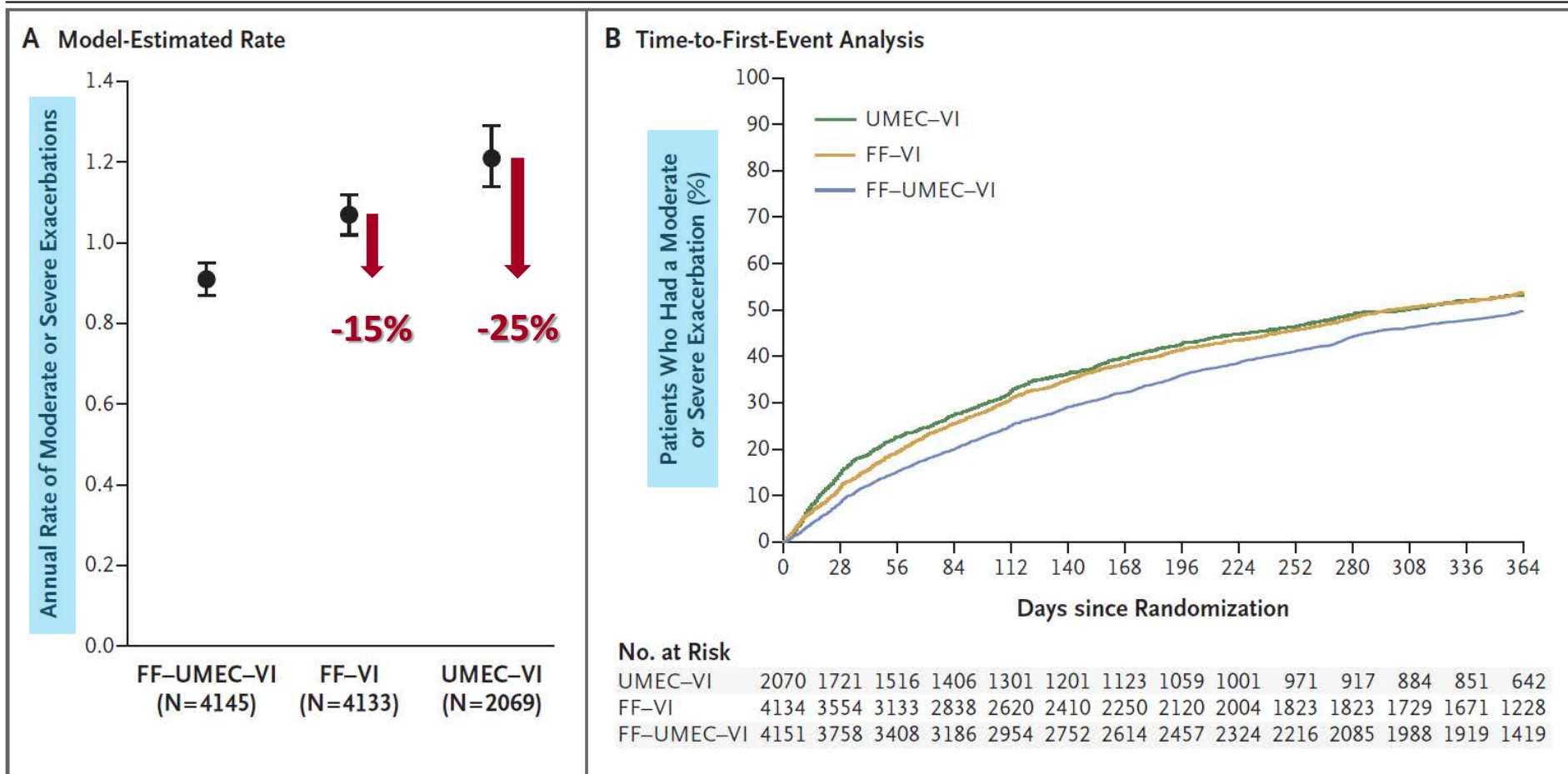


Figure 1. Moderate or Severe COPD Exacerbations (Intention-to-Treat Population).

I bars indicate 95% confidence intervals. COPD denotes chronic obstructive pulmonary disease, FF fluticasone furoate, UMEC umeclidinium, and VI vilanterol.

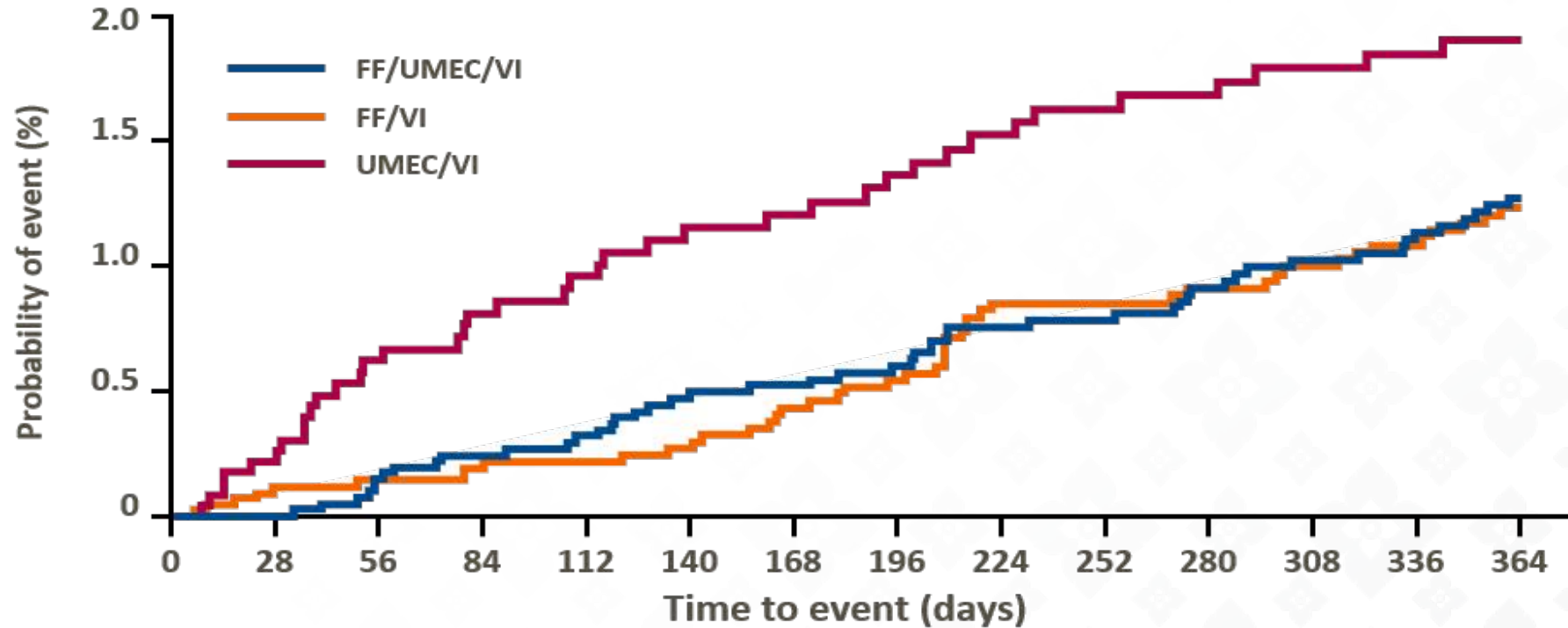


Results

- Mod/severe AECOPD was lower with triple than with either dual, **regardless of eosinophil level**
 - but greater reduction with eosinophils ≥ 150 cells/ μ L
- Higher **trough FEV₁: FF/UMEC/VI** vs FF/VI was 97 mLs [p<0.001], and vs UMEC/VI was 54 mLs [p<0.001]
- **Significant improvement in SGRQ with FF/UMEC/VI**
 - triple therapy -5.5 vs -3.7 and -3.7 (p<0.001)
 - responder analysis: triple 42% vs 34% and 34% (p<0.001)
- **Higher incidence of pneumonia in the ICS groups**
 - FF/UMEC/VI (8%) and FF/VI (7%) vs UMEC/VI (5%)
- **Reduction in all-cause mortality with ICS+ therapies**



All-Cause Mortality



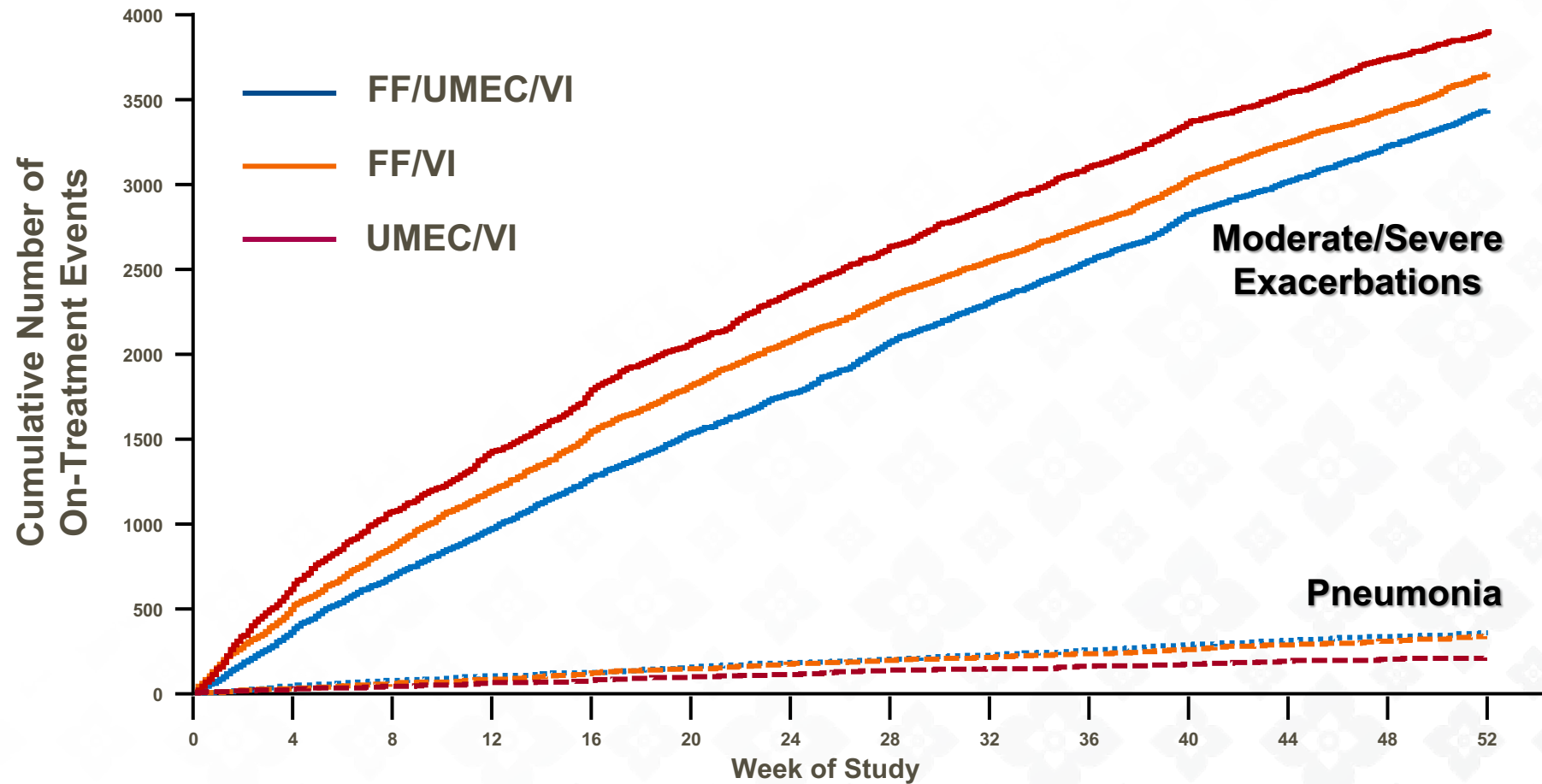
All-cause mortality significantly lower with ICS+ therapy

FF/VI vs UMEC/VI HR 0.61 [0.40-0.93, 39% reduction, p=0.022]

FF/UMEC/VI vs UMEC/VI HR 0.58 [0.38-0.88, 42% reduction, p=0.011]



Moderate/Severe AECOPD vs Pneumonia





'Other' Triple Therapy Studies in COPD

- Papi A, et al. *Lancet* 2018; 391(10125):1076-1084 ['Tribute' trial]
 - *in patients with severe/very severe COPD and an exacerbation history, **BDP/FF/G significantly reduced the rate of moderate/severe AECOPD vs IND/GLY, without increasing the risk of pneumonia***
- Lipson DA, et al. *Am J Resp Crit Care Med* 2017; 196:438-446 ['Fulfil' trial]
 - *results support the **benefits of single-inhaler triple therapy (FF/U/V) compared with ICS/LABA therapy in patients with advanced COPD***
- Ferguson GT, et al. *Lancet Respir Med* 2018; 6:747-758 ['Kronos']
 - ***fixed triple therapy (BDP/Form/Gly) significantly improved lung function vs Gly/Form and Bud/Form (open and closed label) in symptomatic COPD patients receiving 2 or more maintenance therapies***

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

Kenneth R. Chapman^{1*}, John R. Hurst^{2*}, Stefan-Marian Frent^{3‡}, Michael Larbig⁴, Robert Fogel⁵, Tadhg Guerin⁶, Donald Banerji⁵, Francesco Patalano⁴, Pankaj Goyal⁴, Pascal Pfister⁴, Konstantinos Kostikas⁴, and Jadwiga A. Wedzicha⁷

¹Asthma and Airway Centre, University Health Network, University of Toronto, Toronto, Ontario, Canada; ²UCL Respiratory, University College London, London, United Kingdom; ³Department of Pulmonology, University of Medicine and Pharmacy, Timisoara, Romania; ⁴Novartis Pharma AG, Basel, Switzerland; ⁵Novartis Pharmaceuticals Corporation, East Hanover, New Jersey; ⁶Novartis Ireland Limited, Dublin, Ireland; and ⁷Respiratory Clinical Science Section, National Heart and Lung Institute, Imperial College London, London, United Kingdom

Abstract

Rationale: There are no studies on withdrawal of inhaled corticosteroids in patients on long-term triple therapy in the absence of frequent exacerbations.

Objectives: To evaluate the efficacy and safety of direct de-escalation from long-term triple therapy to indacaterol/glycopyrronium in nonfrequently exacerbating patients with chronic obstructive pulmonary disease (COPD).

Methods: This 26-week, randomized, double-blind, triple-dummy study assessed the direct change from long-term triple therapy to indacaterol/glycopyrronium (110/50 µg once daily) or continuation of triple therapy (tiotropium [18 µg] once daily plus combination of salmeterol/fluticasone propionate [50/500 µg] twice daily) in nonfrequently exacerbating patients with moderate-to-severe COPD. Primary endpoint was noninferiority on change from baseline in trough FEV₁. Moderate or severe exacerbations were predefined secondary endpoints.

Measurements and Main Results: A total of 527 patients were randomized to indacaterol/glycopyrronium and 526 to triple therapy. Inhaled corticosteroids withdrawal led to a reduction in trough FEV₁ of -26 ml (95% confidence interval, -53 to 1 ml) with confidence limits exceeding the noninferiority margin of -50 ml. The annualized rate of moderate or severe COPD exacerbations did not differ between treatments (rate ratio, 1.08; 95% confidence interval, 0.83 to 1.40). Patients with ≥300 blood eosinophils/µl at baseline presented greater lung function loss and higher exacerbation risk. Adverse events were similar in the two groups.

Conclusions: In patients with COPD without frequent exacerbations on long-term triple therapy, the direct de-escalation to indacaterol/glycopyrronium led to a small decrease in lung function, with no difference in exacerbations. The higher exacerbation risk in patients with ≥300 blood eosinophils/µl suggests that these patients are likely to benefit from triple therapy.

Clinical trial registered with www.clinicaltrials.gov (NCT 02603393).

Keywords: COPD; indacaterol/glycopyrronium; triple therapy; lung function; exacerbation



Results

- ***“We could not confirm non-inferiority of indacaterol/ glycopyrronium to triple therapy”***
 - **ICS withdrawal led to a reduction in trough FEV₁ -26mLs** (95% CI, -53 to +1 mLs), with confidence limits exceeding non-inferiority margin of -50 mLs
- Annualized **rate of moderate or severe COPD exacerbations did not differ between treatments** indacaterol/ glycopyrronium vs tiotropium + salmeterol/ fluticasone (0.52 vs 0.48; RR 1.08, 95%CI: 0.83 to 1.40)
- Pts with ≥ 300 blood eosinophils/ μ L had significantly greater lung function loss (RR 0.68) and higher AECOPD risk (RR 1.86)
- Adverse events were similar in the two groups



Benefits of Education

- Provides Group Support
- Improves Self-Confidence
- Addresses Family Concerns
- Provides Disease Specific Information
- Improves Risk Factor Awareness
- Helps with Lifestyle Changes



Benefits of Exercise

- Lowers Blood Pressure
- Improves Cholesterol Profile
- Assists with Weight Control
- Helps with Diabetes Prevention and Management
- Improves Quality of Life
- Decreases Stress Level
- Increases Energy Level
- Strengthens Bones



Benefits of Self-management

- Builds confidence
- Promotes ability to take control
- Provides practise on action planning
- Develops problem solving abilities
- Improves symptom management



CDM Program Goals

To develop and implement coordinated, effective and efficient care for people with chronic conditions

To optimize care of people by promoting a team approach and enhanced self-management of disease

To promote inter-professional collaboration and education



Optimizing Chronic Disease Management

For more information about the CDM Program, please contact:

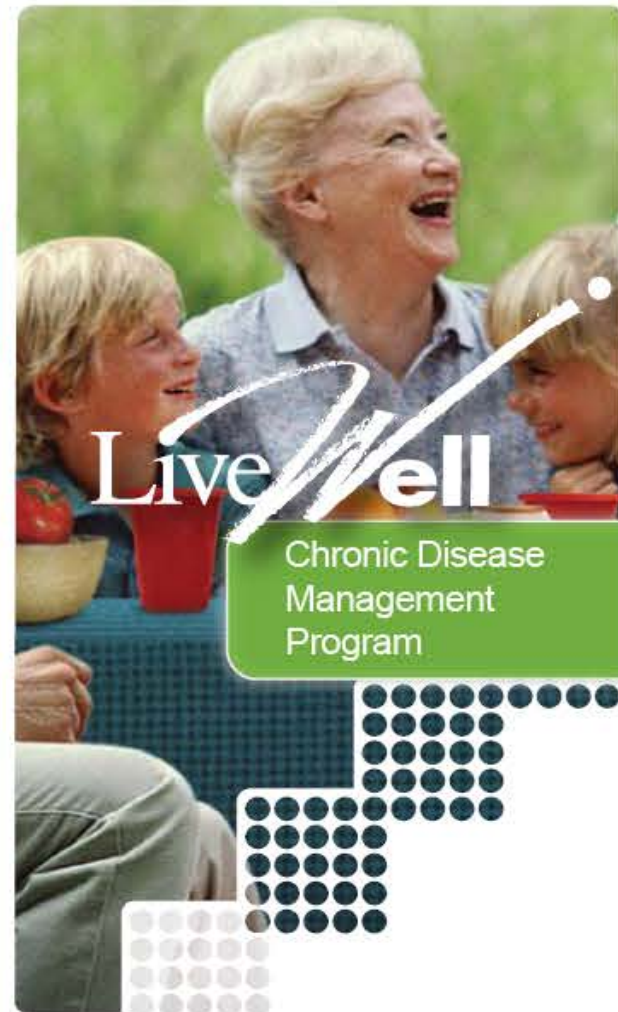
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PROGRAM OF



Live Well

Chronic Disease Management Program

Optimizing Chronic Disease Management

PROGRAM OF



Group Exercise and Rehabilitation

- Community-based exercise and rehabilitation programming
- Group education
- Group and social support

Disease-Specific Management

- Inter-professional team working with the patient, family, and Family Physician
- Evidence-based optimal care delivery

Patient Self-Management

- Individualized plan of action
- Patient-led group support “LiveWell with Chronic Conditions”
- Enhanced self-management skills





Patient Benefits and Outcomes

- **Improved exercise tolerance** (64 m in 6MWD)
- **Improved quality of life**
 - SGRQ reduced by 8.3 (52.9 to 44.6) at 3 months, 5.6 at 6 months, 5.3 at 1 year
- **Decreased healthcare utilization:**
 - COPD re-admissions reduced by 71%, hospital days by 62%, ER visits by 44% at 1 year
 - 3 year follow-up: COPD re-admissions reduced by 64%, hospital days by 29%, ER visits by 30%
- **Improved quality of life, enhanced exercise tolerance, reduced exacerbations and hospitalizations, and reduced healthcare costs ('cost-dominant').**

A Comprehensive Care Management Program to Prevent Chronic Obstructive Pulmonary Disease Hospitalizations

A Randomized, Controlled Trial

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Background: Improving a patient's ability to self-monitor and manage changes in chronic obstructive pulmonary disease (COPD) symptoms may improve outcomes.

Objective: To determine the efficacy of a comprehensive care management program (CCMP) in reducing the risk for COPD hospitalization.

Design: A randomized, controlled trial comparing CCMP with guideline-based usual care. (ClinicalTrials.gov registration number: NCT00395083)

Setting: 20 Veterans Affairs hospital-based outpatient clinics.

Participants: Patients hospitalized for COPD in the past year.

Intervention: The CCMP included COPD education during 4 individual sessions and 1 group session, an action plan for identification and treatment of exacerbations, and scheduled proactive telephone calls for case management. Patients in both the intervention and usual care groups received a COPD informational booklet; their primary care providers received a copy of COPD guidelines and were advised to manage their patients according to these guidelines. Patients were randomly assigned, stratifying by site based on random, permuted blocks of variable size.

Measurements: The primary outcome was time to first COPD hospitalization. Staff blinded to study group performed telephone-based assessment of COPD exacerbations and hospitalizations, and all hospitalizations were blindly adjudicated. Secondary outcomes included non-COPD health care use, all-cause mortality, health-related quality of life, patient satisfaction, disease knowledge, and self-efficacy.

Results: Of the eligible patients, 209 were randomly assigned to the intervention group and 217 to the usual care group. Citing serious safety concerns, the data monitoring committee terminated the intervention before the trial's planned completion after 426 (44%) of the planned total of 960 patients were enrolled. Mean follow-up was 250 days. When the study was stopped, the 1-year cumulative incidence of COPD-related hospitalization was 27% in the intervention group and 24% in the usual care group (hazard ratio, 1.13 [95% CI, 0.70 to 1.80]; $P = 0.62$). There were 28 deaths from all causes in the intervention group versus 10 in the usual care group (hazard ratio, 3.00 [CI, 1.46 to 6.17]; $P = 0.003$). Cause could be assigned in 27 (71%) deaths. Deaths due to COPD accounted for the largest difference: 10 in the intervention group versus 3 in the usual care group (hazard ratio, 3.60 [CI, 0.99 to 13.08]; $P = 0.053$).

Limitations: Available data could not fully explain the excess mortality in the intervention group. Ability to assess the quality of the educational sessions provided by the case managers was limited.

Conclusion: A CCMP in patients with severe COPD had not decreased COPD-related hospitalizations when the trial was stopped prematurely. The CCMP was associated with unanticipated excess mortality, results that differ markedly from similar previous trials. A data monitoring committee should be considered in the design of clinical trials involving behavioral interventions.

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For author affiliations, see end of text.

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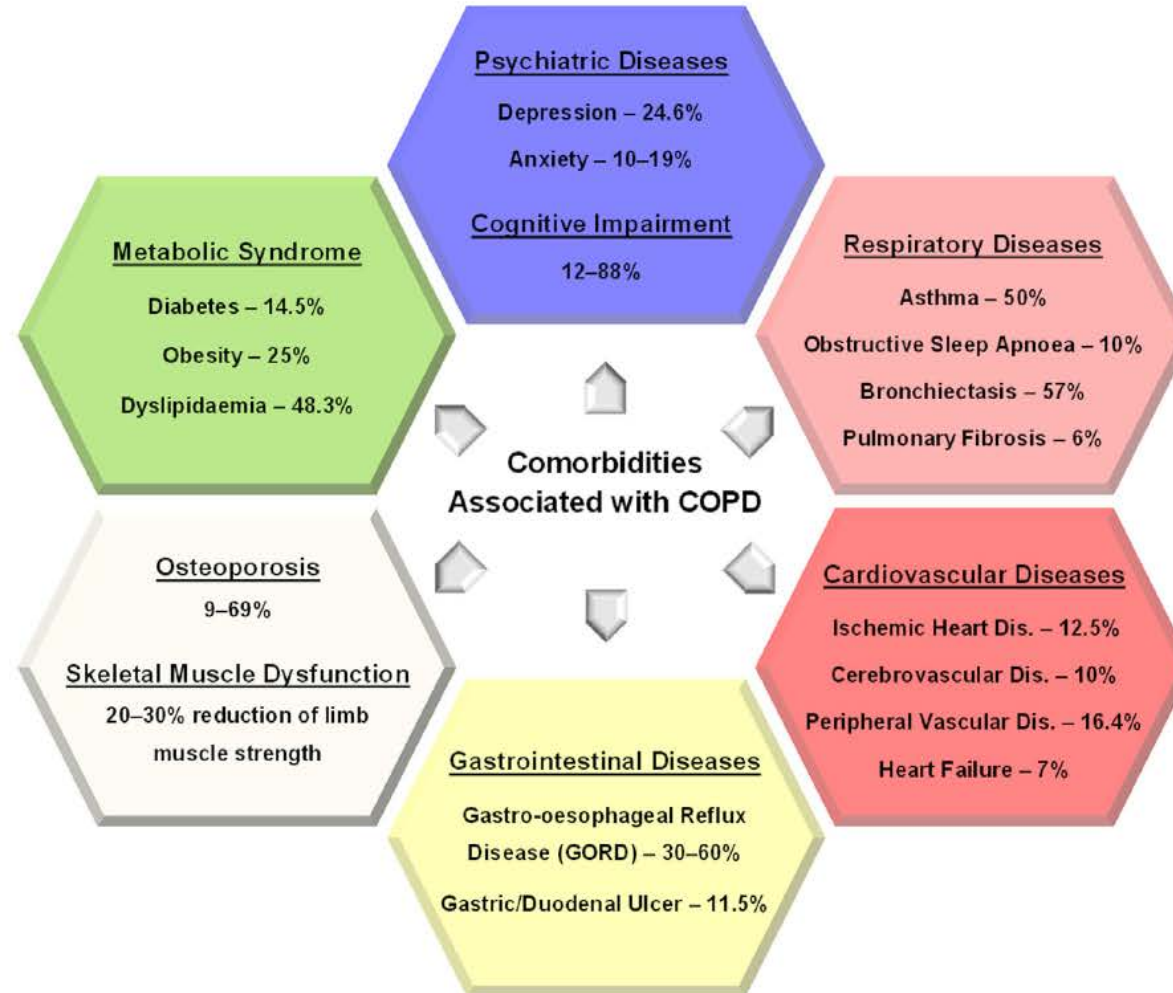


Unexpected Results!

- **study terminated early - increased mortality** in CC group [28 deaths vs 10 in UC group; $p = 0.003$]
 - 'COPD' deaths accounted for the difference
- **delay in starting prednisone treatment** (6.4 CC vs 7.7 days UC; $p = 0.48$) and **delay in starting antibiotic treatment** (7.0 days CC vs 6.8 days UC ; $p = 0.84$)
 - **fundamental failure of the intervention!**
- **staff had varied backgrounds, with [only] 3 training days**
 - patients with complex COPD and high disease burden require specialized attention and expertise
- **uncertain goal of the intervention ...**
 - 'keep away from the ER' vs 'best care at the earliest time'



COPD Comorbidities and Coexistent Conditions



A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (LIBERATE)

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Abstract

Rationale: This is the first multicenter randomized controlled trial to evaluate the effectiveness and safety of Zephyr Endobronchial Valve (EBV) in patients with little to no collateral ventilation out to 12 months.

Objectives: To evaluate the effectiveness and safety of Zephyr EBV in heterogeneous emphysema with little to no collateral ventilation in the treated lobe.

Methods: Subjects were enrolled with a 2:1 randomization (EBV/standard of care [SoC]) at 24 sites. Primary outcome at 12 months was the Δ EBV–SoC of subjects with a post-bronchodilator FEV₁ improvement from baseline of greater than or equal to 15%. Secondary endpoints included absolute changes in post-bronchodilator FEV₁, 6-minute-walk distance, and St. George's Respiratory Questionnaire scores.

Measurements and Main Results: A total of 190 subjects (128 EBV and 62 SoC) were randomized. At 12 months, 47.7% EBV and 16.8% SoC subjects had a Δ FEV₁ greater than or equal to 15% ($P <$

0.001). Δ EBV–SoC at 12 months was statistically and clinically significant: for FEV₁, 0.106 L ($P < 0.001$); 6-minute-walk distance, +39.31 m ($P = 0.002$); and St. George's Respiratory Questionnaire, –7.05 points ($P = 0.004$). Significant Δ EBV–SoC were also observed in hyperinflation (residual volume, –522 ml; $P < 0.001$), modified Medical Research Council Dyspnea Scale (–0.8 points; $P < 0.001$), and the BODE (body mass index, airflow obstruction, dyspnea, and exercise capacity) index (–1.2 points). Pneumothorax was the most common serious adverse event in the treatment period (procedure to 45 d), in 34/128 (26.6%) of EBV subjects. Four deaths occurred in the EBV group during this phase, and one each in the EBV and SoC groups between 46 days and 12 months.

Conclusions: Zephyr EBV provides clinically meaningful benefits in lung function, exercise tolerance, dyspnea, and quality of life out to at least 12 months, with an acceptable safety profile in patients with little or no collateral ventilation in the target lobe.

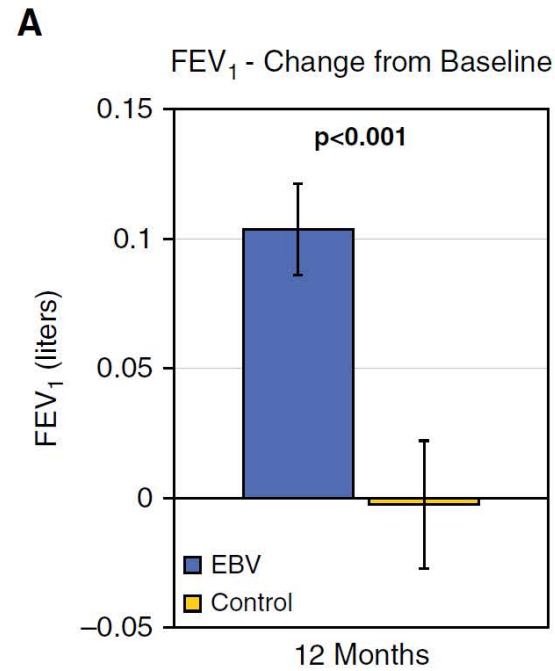
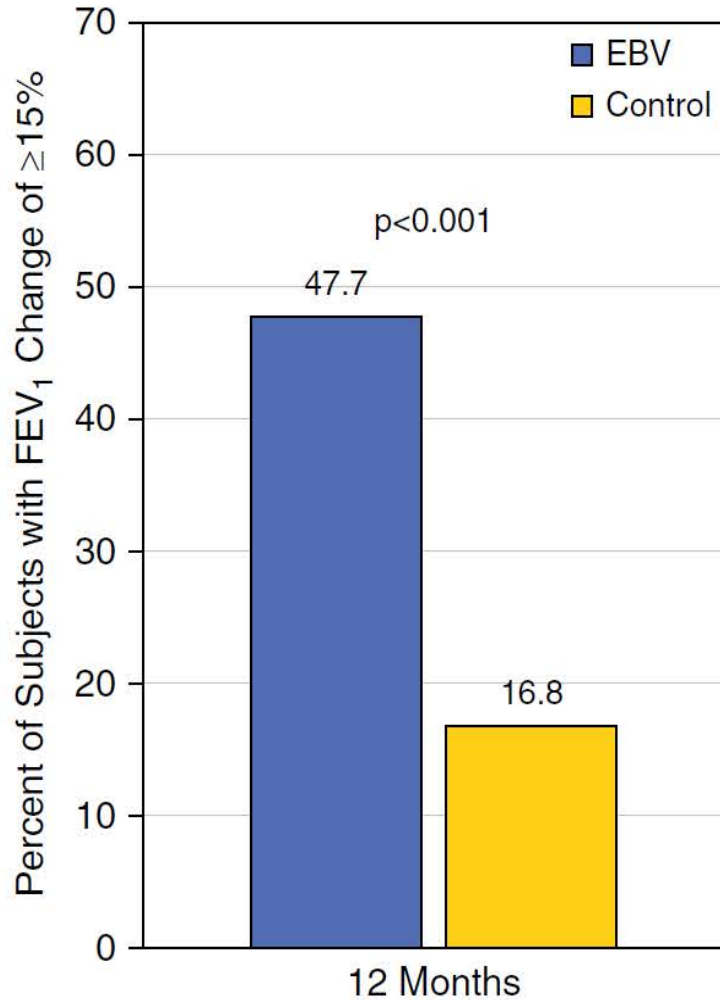
Clinical trial registered with www.clinicaltrials.gov (NCT01796392).

Keywords: chronic obstructive pulmonary disease; emphysema; lung reduction

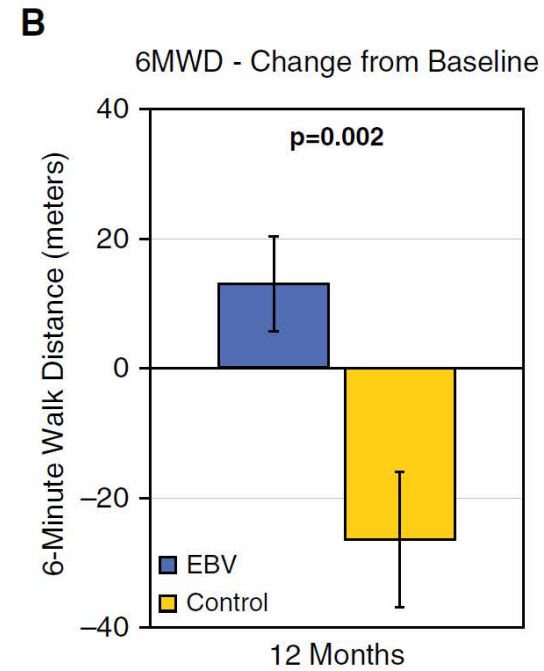
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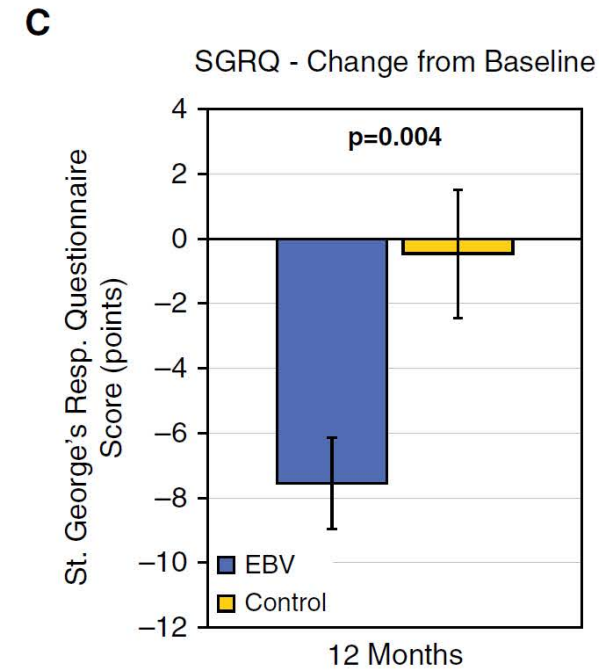
Results



106 mLs



39.3 m



-7.1 u

Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation

A Randomized Clinical Trial

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IMPORTANCE Outcomes after exacerbations of chronic obstructive pulmonary disease (COPD) requiring acute noninvasive ventilation (NIV) are poor and there are few treatments to prevent hospital readmission and death.

OBJECTIVE To investigate the effect of home NIV plus oxygen on time to readmission or death in patients with persistent hypercapnia after an acute COPD exacerbation.

DESIGN, SETTING, AND PARTICIPANTS A randomized clinical trial of patients with persistent hypercapnia ($\text{PaCO}_2 > 53$ mm Hg) 2 weeks to 4 weeks after resolution of respiratory acidemia, who were recruited from 13 UK centers between 2010 and 2015. Exclusion criteria included obesity (body mass index [BMI] > 35), obstructive sleep apnea syndrome, or other causes of respiratory failure. Of 2021 patients screened, 124 were eligible.

INTERVENTIONS There were 59 patients randomized to home oxygen alone (median oxygen flow rate, 1.0 L/min [interquartile range {IQR}, 0.5-2.0 L/min]) and 57 patients to home oxygen plus home NIV (median oxygen flow rate, 1.0 L/min [IQR, 0.5-1.5 L/min]). The median home ventilator settings were an inspiratory positive airway pressure of 24 (IQR, 22-26) cm H_2O , an expiratory positive airway pressure of 4 (IQR, 4-5) cm H_2O , and a backup rate of 14 (IQR, 14-16) breaths/minute.

MAIN OUTCOMES AND MEASURES Time to readmission or death within 12 months adjusted for the number of previous COPD admissions, previous use of long-term oxygen, age, and BMI.

RESULTS A total of 116 patients (mean [SD] age of 67 [10] years, 53% female, mean BMI of 21.6 [IQR, 18.2-26.1], mean [SD] forced expiratory volume in the first second of expiration of 0.6 L [0.2 L], and mean [SD] PaCO_2 while breathing room air of 59 [7] mm Hg) were randomized. Sixty-four patients (28 in home oxygen alone and 36 in home oxygen plus home NIV) completed the 12-month study period. The median time to readmission or death was 4.3 months (IQR, 1.3-13.8 months) in the home oxygen plus home NIV group vs 1.4 months (IQR, 0.5-3.9 months) in the home oxygen alone group, adjusted hazard ratio of 0.49 (95% CI, 0.31-0.77; $P = .002$). The 12-month risk of readmission or death was 63.4% in the home oxygen plus home NIV group vs 80.4% in the home oxygen alone group, absolute risk reduction of 17.0% (95% CI, 0.1%-34.0%). At 12 months, 16 patients had died in the home oxygen plus home NIV group vs 19 in the home oxygen alone group.

CONCLUSIONS AND RELEVANCE Among patients with persistent hypercapnia following an acute exacerbation of COPD, adding home noninvasive ventilation to home oxygen therapy prolonged the time to readmission or death within 12 months.

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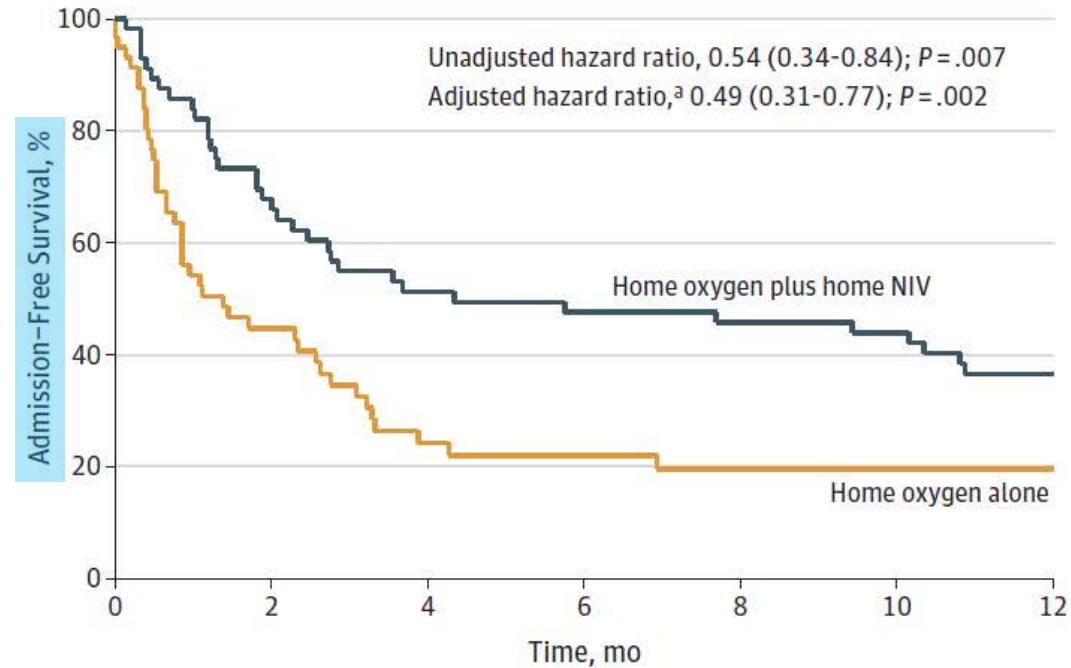
Author Affiliations: Author affiliations are listed at the end of this article.

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Time to Re-Admission or Death



No. at risk	0	2	4	6	8	10	12
Home oxygen plus home NIV	57	37	28	26	25	24	16
Home oxygen alone	59	23	11	10	8	8	6

Median **time to readmission or death** in NIV+O₂ group was **4.3 months** vs **1.4 months** in O₂ group (adjusted HR 0.49, 95% CI 0.31-0.77; p=0.002). **12-month risk of readmission or death** was 63.4% in the NIV+O₂ group vs 80.4% in the O₂ group (absolute risk reduction **17.0%**; 95%CI 0.1%-34.0%)



Closing Thoughts ...

- COPD places a significant burden on patients and their families, as well as on our healthcare system
- Research continues to enhance our understanding, and there have been refinements in recent position statements and evidence-based guidelines [GOLD, and CTS Pharmacotherapy in Patients with COPD]
- We genuinely have many **effective pharmacologic, non-pharmacologic, and healthcare system interventions and strategies to improve the care and outcomes for patients suffering from COPD**



Justin Moore
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