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COPD Year in Review

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By the end of this presentation …

- Appreciate the evolving role of **triple inhaled therapy** (LABA/LABA/ICS) in the management of stable COPD
- Recognize the [dis]advantages of [not] **appropriately diagnosing COPD**
- Understand whether early **treatment of mild and moderate COPD makes a difference**
- Identify the potential role, benefits, and adverse consequences of **endobronchial valve insertion** in patients with advanced COPD
- Acknowledge the role of **home NIV and O_2 therapy** in the long-term management of stable COPD patients following severe AECOPD

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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AstraZeneca, Boehringer Ingelheim, Canada Health Infoway, Canadian Institute of Health Research, GlaxoSmithKline, Lung Association of Saskatchewan, Lung Health Institute of Canada, Novartis, Sanofi, Saskatchewan Health Research Foundation, Schering-Plough

Employee

University of Saskatchewan

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

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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.)

Lipson DA, et al.
***N Engl J Med* 2018;**
378:1671-1680

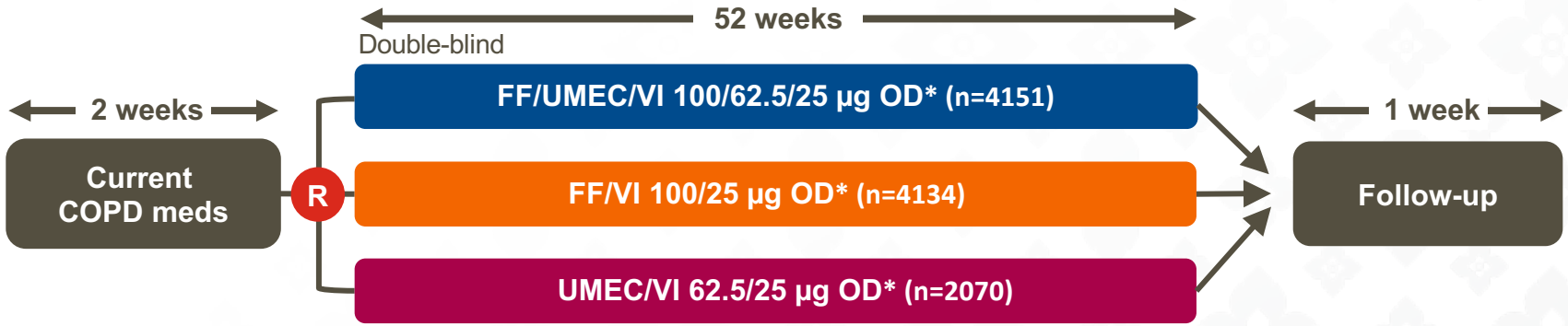
Background

- 'Triple Therapy' (**ICS/LABA/LAMA**) is recommended in the GOLD (and Canadian Thoracic Society - CTS) management strategy for COPD in patients who have clinically significant symptoms despite treatment with ICS/LABA or LABA/LAMA, and who are at increased risk for frequent or severe exacerbations
- Prior studies have shown **triple inhaled therapy has positive effects on lung function and symptoms compared with dual therapy**
- But there are limitations with prior work, **few direct prospective comparisons**, and thus questions about incremental benefit persist

Lipson DA, et al. *N Engl J Med* 2018; 378:1671-1680

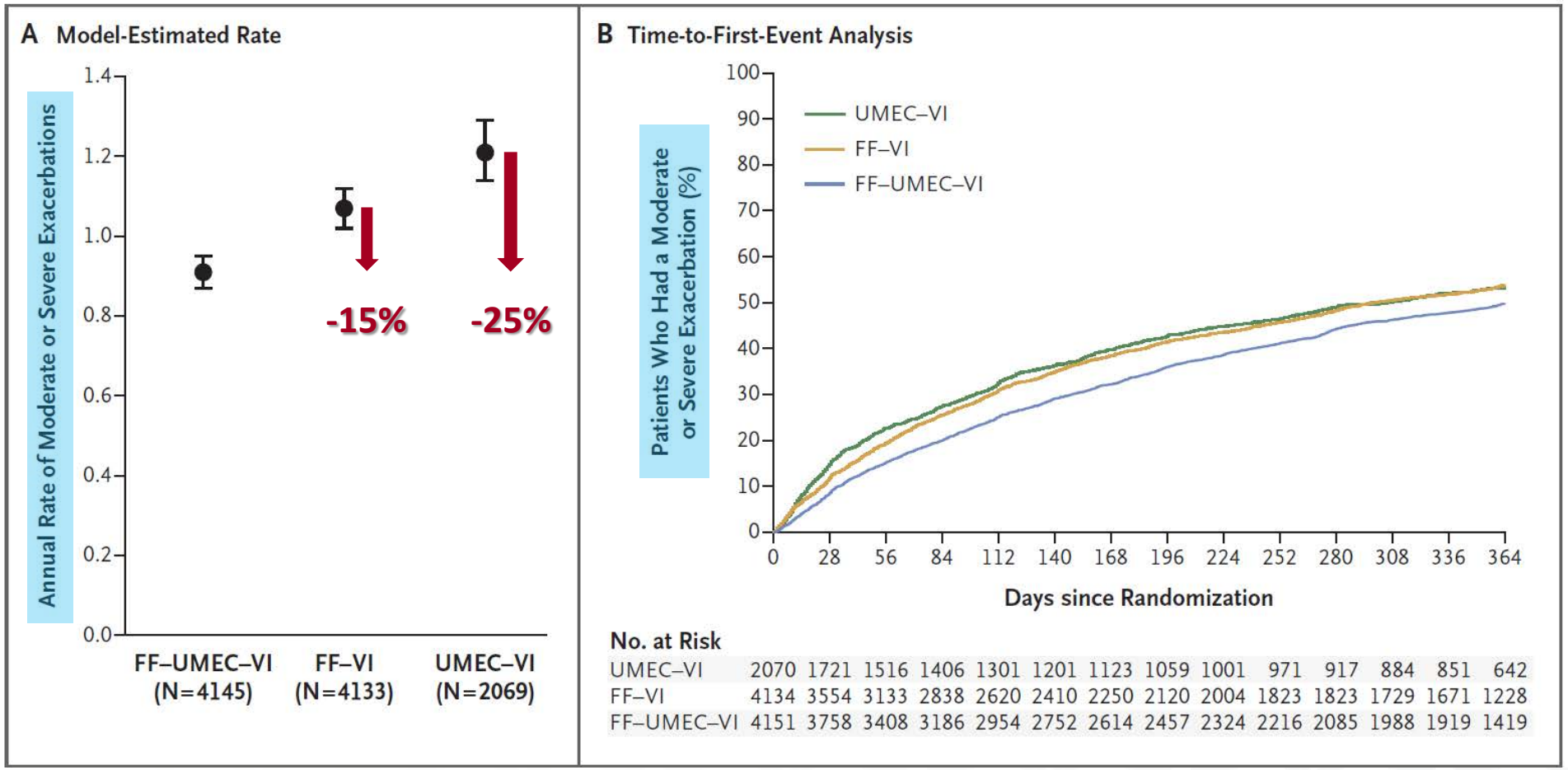
Methods

- Phase 3, randomized, double-blinded, parallel-group, multicenter trial (37 countries)
  - n=10,355, **CAT ≥10, FEV_1 ≤50% pred with ≥1 AECOPD in prior 1 year or FEV_1 50 - 80% pred with ≥2 moderate or ≥1 severe AECOPD** (hospitalization)



- Co-1^0 endpoint **moderate or severe AECOPD** vs FF/VI and vs UMEC/VI. Key 2^o endpoints include trough **FEV_1, SGRQ, time to mod/severe AECOPD, and mortality**

Lipson DA, et al. *N Engl J Med* 2018; 378:1671-1680



And decreased **severe AECOPD (hospitalization): FF/UMEC/VI** (0.13/yr) vs FF/VI (0.15/yr) [**13%**, p=0.06] and vs UMEC/VI (0.19/yr) [**34%**, p<0.001]

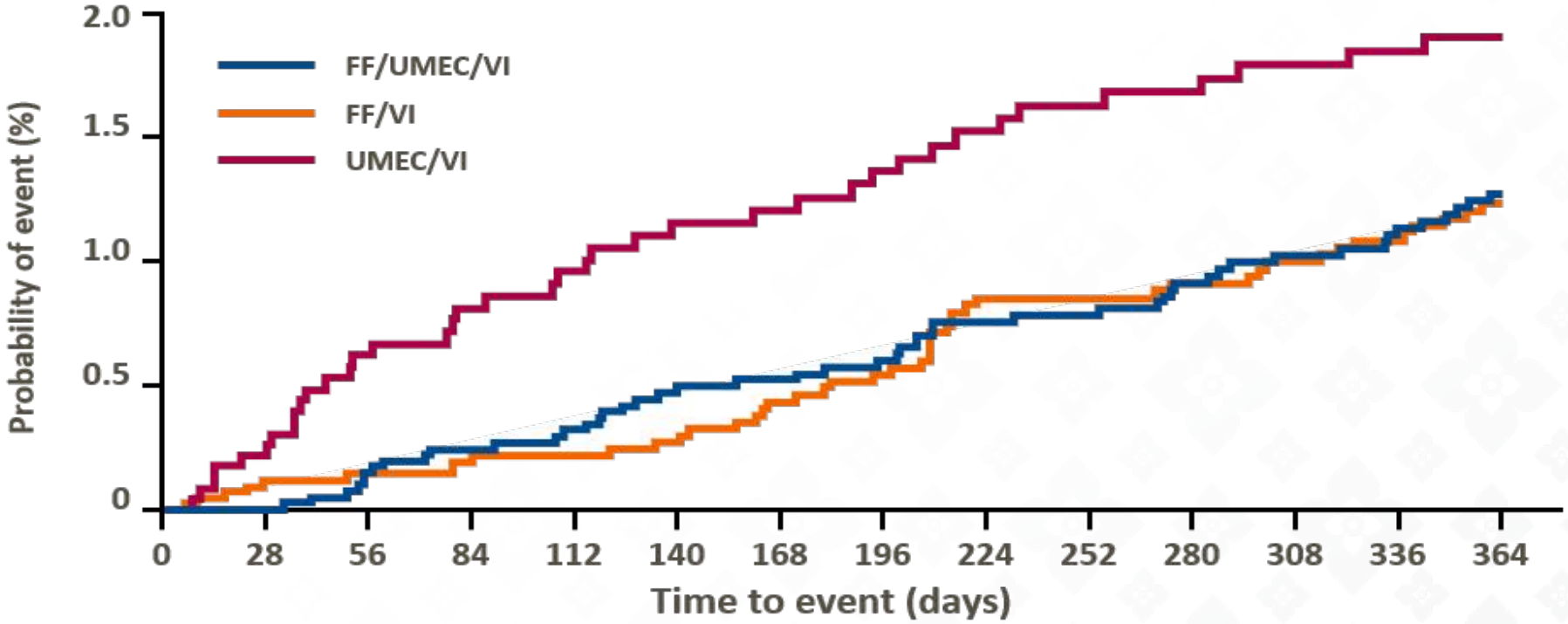
Lipson DA, et al. *N Engl J Med* 2018; 378:1671-1680

Results

- Mod/severe AECOPD was lower with triple than with either dual, **regardless of eosinophil level**
  - but greater reduction with eosinophils ≥ 150 cells/µL
- Higher **trough FEV_1: 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**

Lipson DA, et al. *N Engl J Med* 2018; 378:1671-1680

All-Cause Mortality



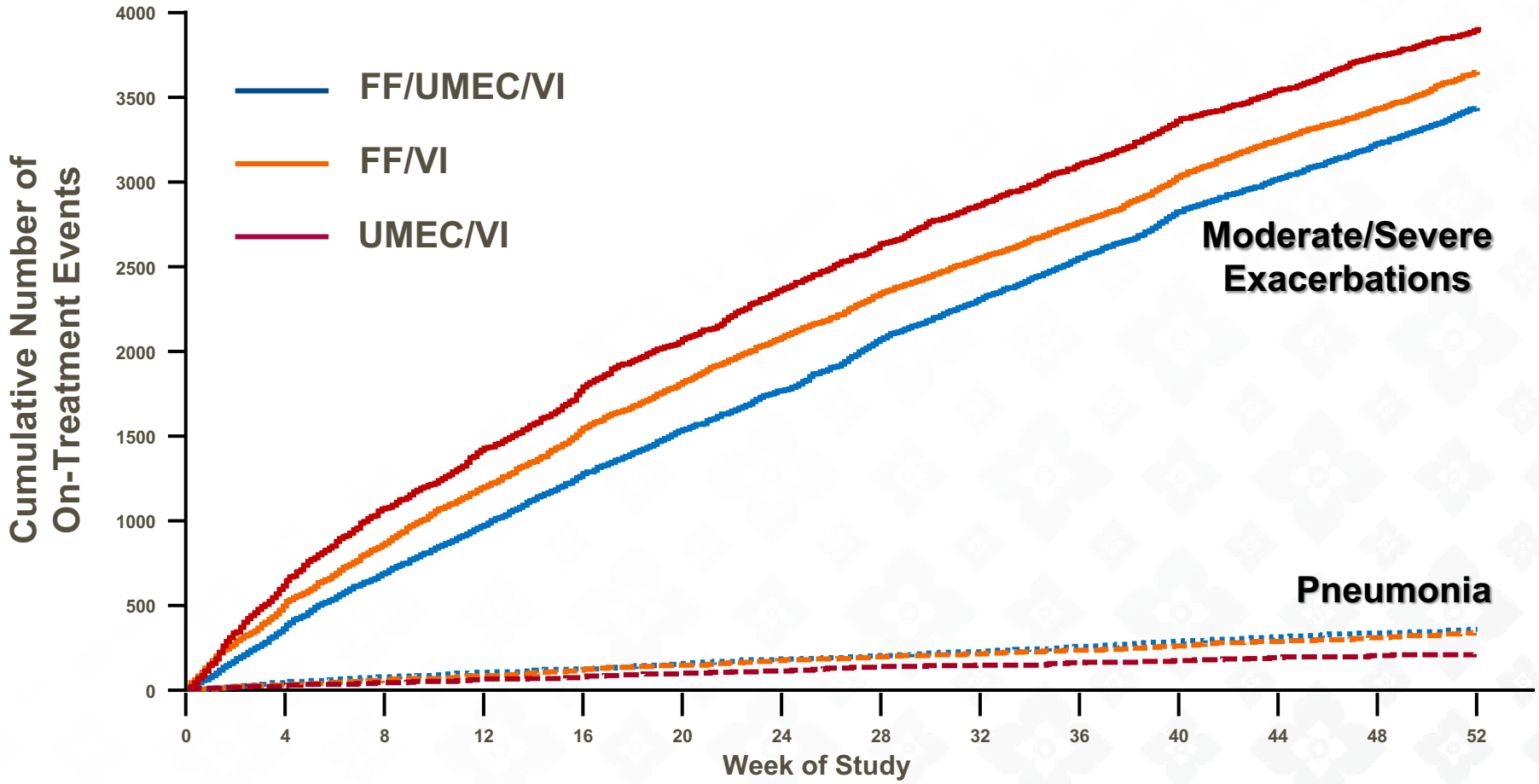
All-cause mortality significantly lower with ICS+ therapy

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**]

Lipson DA, et al. *N Engl J Med* 2018; 378:1671-1680

Moderate/Severe AECOPD vs Pneumonia



Lipson DA, et al. *N Engl J Med* 2018; 378:1671-1680, and ATS May 2018.

Observations

- In this COPD population, **triple therapy significantly decreased moderate/severe AECOPD compared to FF/VI and UMEC/VI (and significantly less hospitalizations)**
- While pneumonia was more frequent in the ICS+ therapy, absolute rates >10x less than AECOPD
  - **reduction in all-cause mortality with ICS+ therapies**
- 'Other' Triple Therapy Studies
  - Papi A, et al. *Lancet* 2018, '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. *AJRCCM* 2017, 'Fulfil' trial. *Results support* ***benefits of single-inhaler triple therapy (FF/U/V) compared with ICS/LABA therapy in advanced COPD***

Lipson DA, et al. *N Engl J Med* 2018; 378:1671-1680

Prognosis of asymptomatic and symptomatic, undiagnosed COPD in the general population in Denmark: a prospective cohort study

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Lancet Respir Med 2017; 5: 426–34

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See Comment page 367

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Summary

Background COPD can be diagnosed early using spirometry, but spirometry use is only recommended in symptomatic smokers, even though early stages of COPD can be asymptomatic. We investigated the prognosis of individuals with asymptomatic and symptomatic, undiagnosed COPD in the general population in Denmark.

Methods In this prospective cohort study, we analysed data from 95 288 individuals aged 20–100 years from the Copenhagen General Population Study. 32 518 (34%) of these individuals were regarded as being at high risk for COPD (defined as individuals aged 40 years or older, with cumulative tobacco consumption of ten pack-years or higher, and without self-reported or a previous hospital contact for asthma). COPD was defined as FEV_1/forced vital capacity (FVC) of less than 70% and less than the lower limit of normal, and FEV_1 of less than 80% of the predicted normal value. Individuals were considered undiagnosed if neither a previous COPD hospital contact, nor medical treatment for COPD, was registered. We obtained information on exacerbations and pneumonia from the National Danish Patient Registry and vital status from the National Danish Civil Registration System, and cause of death from the National Danish Causes of Death Registry. We used Cox proportional hazard models to assess risk of exacerbations, pneumonia, deaths due to respiratory causes, and deaths from all causes from 2003 to 2014.

Findings Between Nov 26, 2003, and July 10, 2013, 95 288 individuals were screened and 32 518 (34%) were at high risk of having COPD. 3699 (11%) of these participants met the COPD criteria and 2903 (78%) were undiagnosed, of whom 2052 (71%) were symptomatic. During a median follow-up of 6·1 years (IQR 4·9), we recorded 800 exacerbations, 2038 cases of pneumonia, and 2789 deaths in the 32 518 individuals at high risk of having COPD, including 152 deaths due to respiratory disease. Compared with individuals without COPD, the age and sex adjusted hazard ratio (HR) was 5·0 (95% CI 2·8–8·9) for exacerbations, 1·7 (1·3–2·2) for pneumonia, 0·7 (0·2–3·0) for death from respiratory causes, and 1·3 (1·1–1·6) for death from all causes in individuals with undiagnosed, asymptomatic COPD. Corresponding HRs were 15·5 (11·0–21·8) for exacerbations, 2·8 (2·4–3·3) for pneumonia, 4·3 (2·8–6·7) for death from respiratory causes, and 2·0 (1·8–2·3) for death from all causes in individuals with undiagnosed, symptomatic COPD.

Interpretation Individuals with undiagnosed, symptomatic COPD had an increased risk of exacerbations, pneumonia, and death. Individuals with undiagnosed, asymptomatic COPD had an increased risk of exacerbations and pneumonia. These findings suggest that better initiatives for early diagnosis and treatment of COPD are needed.

Funding The Danish Lung Association, the Danish Cancer Society, Herlev and Gentofte Hospital, Copenhagen University Hospital, and University of Copenhagen.

Colak Y, et al.
***Lancet Respir Med* 2017;**
5:426-434

Background

- COPD can be diagnosed early using spirometry, but **spirometry use is only 'recommended' in symptomatic smokers [even though early stages of COPD may/can be asymptomatic]**
- Prior random-sampled population studies have demonstrated that **~70% of COPD is 'undiagnosed'**[1]
  - **associated with a significant burden of healthcare use**
- Wished to explore the prognosis of individuals with asymptomatic and symptomatic, undiagnosed COPD in the general population in Denmark

Colak Y, et al. *Lancet Respir Med* 2017; 5:426-434

Methods

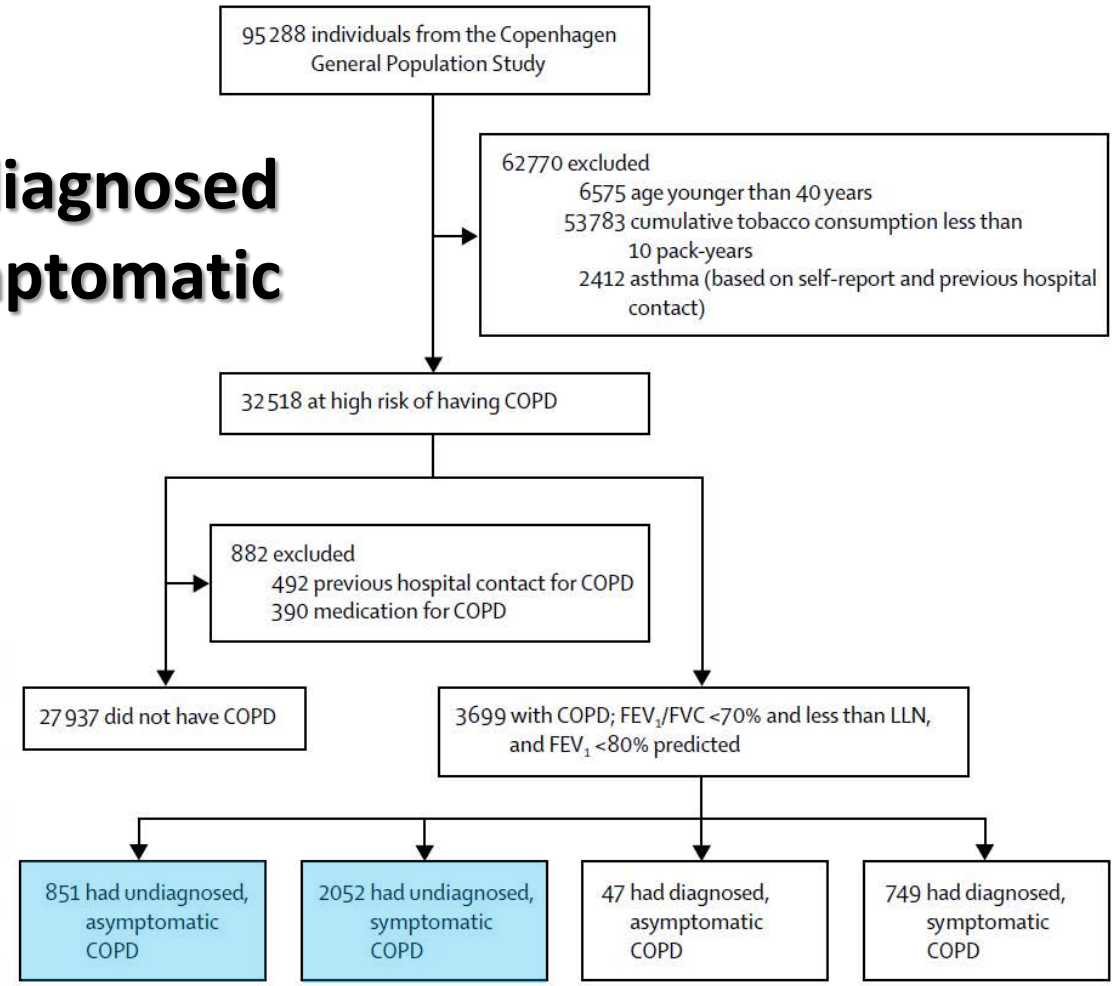
- Prospective cohort study (Copenhagen General Population Study), n=95,288, aged 20–100 yrs
  - 32,518 (34%) regarded as high risk for COPD **(defined as ≥40 yrs with smoking ≥10 pack-yrs, and without self-reported or prior hospital asthma contact)**
- **COPD defined FEV_1/FVC <70% predicted and <LLN, with FEV_1 <80% predicted**
- Individuals considered undiagnosed if neither a previous COPD hospital contact nor medical treatment for COPD was registered
- Linked data (2003-2014) on exacerbations, pneumonia, deaths due to respiratory causes, and all cause deaths
  - Danish Patient Registry, Danish Civil Registration System, and Danish Causes of Death Registry

Colak Y, et al. *Lancet Respir Med* 2017; 5:426-434

CONSORT Study Profile

78% undiagnosed

71% symptomatic

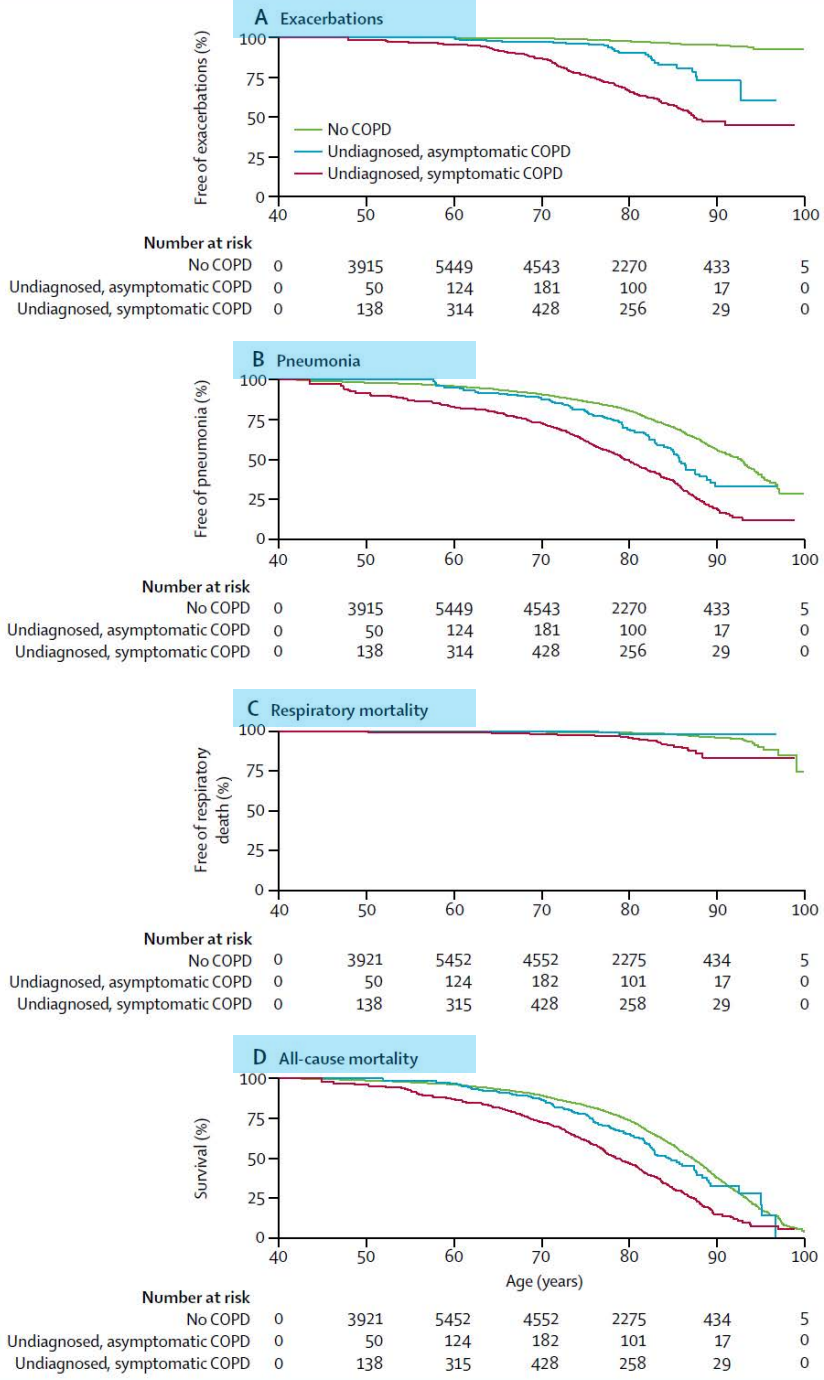


Colak Y, et al. *Lancet Respir Med* 2017; 5:426-434

Results

- 3699 **(11%) of participants met the COPD criteria**, with median **follow-up of 6.1 yrs**
  - 2903 **(78%) were undiagnosed, of whom 2052 (71%) were symptomatic** (FEV_1 66% predicted)
- Compared to individuals without COPD, **undiagnosed <u>symptomatic</u> COPD:**
  - age and sex-adjusted HR of 15.5 (95% CI 11.0–21.8) for exacerbations, 2.8 (2.4–3.3) for pneumonia, 4.3 (2.8–6.7) for death from respiratory causes, and 2.0 (1.8–2.3) for death from all causes
- Compared to individuals without COPD, **undiagnosed <u>asymptomatic</u> COPD:**
  - age and sex-adjusted HR of 5.0 (2.8–8.9) for exacerbations, and 1.7 (1.3–2.2) for pneumonia

Colak Y, et al. *Lancet Respir Med* 2017; 5:426-434



Kaplan-Meier curves for risk of AECOPD, pneumonia, respiratory mortality, and all-cause mortality in individuals with undiagnosed COPD

Colak Y, et al. *Lancet Respir Med* 2017; 5:426-434

Observations

- Individuals with undiagnosed, symptomatic COPD had an increased risk of exacerbations, pneumonia, and death
- Individuals with undiagnosed, asymptomatic COPD had an increased risk of exacerbations and pneumonia
- **Important to appropriately diagnose COPD?**
  - **[extremely] high prevalence of under-diagnosis in COPD,** and the observed **poor prognosis in individuals with undiagnosed COPD**, highlights the importance of implementation of better initiatives for the early[ier] diagnosis and treatment of COPD

Colak Y, et al. *Lancet Respir Med* 2017; 5:426-434

Tiotropium in Early-Stage Chronic Obstructive Pulmonary Disease

Y. Zhou, N. Zhong, Xiaochen Li, S. Chen, J. Zheng, D. Zhao, W. Yao, R. Zhi, L. Wei, B. He, X. Zhang, C. Yang, Ying Li, F. Li, J. Du, J. Gui, B. Hu, C. Bai, P. Huang, G. Chen, Y. Xu, C. Wang, B. Liang, Yinhuan Li, G. Hu, H. Tan, X. Ye, X. Ma, Y. Chen, X. Hu, J. Tian, X. Zhu, Z. Shi, X. Du, M. Li, S. Liu, R. Yu, J. Zhao, Q. Ma, C. Xie, Xiongbin Li, T. Chen, Y. Lin, Lizhen Zeng, C. Ye, W. Ye, X. Luo, Lingshan Zeng, S. Yu, W. Guan, and P. Ran

ABSTRACT

BACKGROUND

Patients with mild or moderate chronic obstructive pulmonary disease (COPD) rarely receive medications, because they have few symptoms. We hypothesized that long-term use of tiotropium would improve lung function and ameliorate the decline in lung function in patients with mild or moderate COPD.

METHODS

In a multicenter, randomized, double-blind, placebo-controlled trial that was conducted in China, we randomly assigned 841 patients with COPD of Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 1 (mild) or 2 (moderate) severity to receive a once-daily inhaled dose (18 μg) of tiotropium (419 patients) or matching placebo (422) for 2 years. The primary end point was the between-group difference in the change from baseline to 24 months in the forced expiratory volume in 1 second (FEV_1) before bronchodilator use. Secondary end points included the between-group difference in the change from baseline to 24 months in the FEV_1 after bronchodilator use and the between-group difference in the annual decline in the FEV_1 before and after bronchodilator use from day 30 to month 24.

RESULTS

Of 841 patients who underwent randomization, 388 patients in the tiotropium group and 383 in the placebo group were included in the full analysis set. The FEV_1 in patients who received tiotropium was higher than in those who received placebo throughout the trial (ranges of mean differences, 127 to 169 ml before bronchodilator use and 71 to 133 ml after bronchodilator use; P<0.001 for all comparisons). There was no significant amelioration of the mean (±SE) annual decline in the FEV_1 before bronchodilator use: the decline was 38±6 ml per year in the tiotropium group and 53±6 ml per year in the placebo group (difference, 15 ml per year; 95% confidence interval [CI], −1 to 31; P=0.06). In contrast, the annual decline in the FEV_1 after bronchodilator use was significantly less in the tiotropium group than in the placebo group (29±5 ml per year vs. 51±6 ml per year; difference, 22 ml per year [95% CI, 6 to 37]; P=0.006). The incidence of adverse events was generally similar in the two groups.

CONCLUSIONS

Tiotropium resulted in a higher FEV_1 than placebo at 24 months and ameliorated the annual decline in the FEV_1 after bronchodilator use in patients with COPD of GOLD stage 1 or 2. (Funded by Boehringer Ingelheim and others; Tie-COPD ClinicalTrials.gov number, NCT01455129.)

Zhou Y, et al.
***N Engl J Med* 2017;**
377:923-935

Background

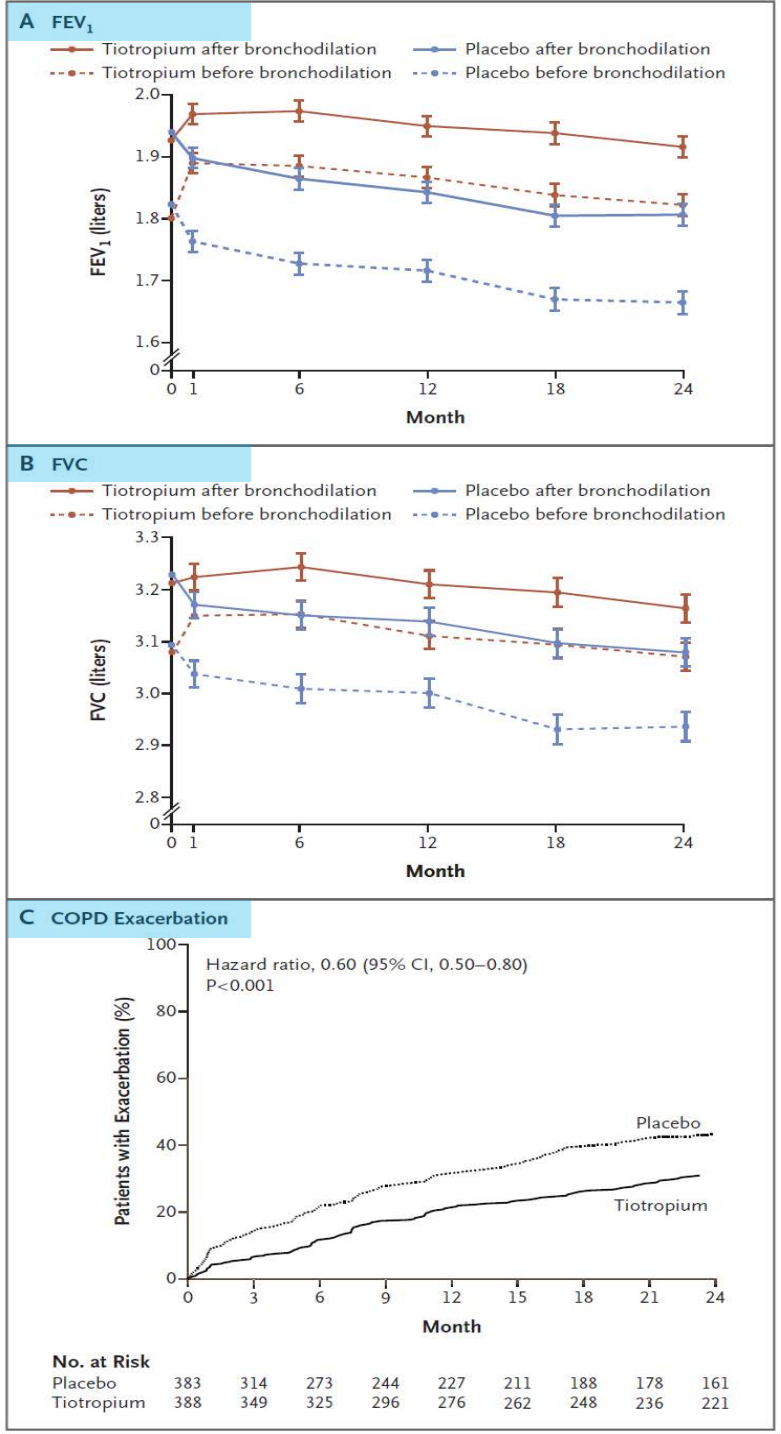
- **Patients with mild or moderate COPD rarely receive medications**, because they either have few symptoms, or are not diagnosed, or …
- Evidence of 'benefit' has been conflicting and/or modest in the mild COPD population
- Hypothesized that long-term long-acting bronchodilator therapy (tiotropium) would improve lung function and ameliorate the decline in lung function in patients with mild or moderate COPD

Zhou Y, et al. *N Engl J Med* 2017; 377:923-935

Methods

- Multicenter (all sites in China), randomized, double-blind, placebo-controlled trial, n = 841 subjects with GOLD stage 1 (mild) or 2 (moderate) COPD
- Tiotropium 18 OD vs matching placebo for 2 yrs
- 1º endpoint was **between-group difference in change from baseline to 24 months in trough FEV_1**
  - 2^0 endpoints were between-group difference in change from baseline to 24 months in **post-bronchodilator FEV_1** and between-group difference in **annual decline in FEV_1 before and after bronchodilator** from day 30 to month 24

Zhou Y, et al. *N Engl J Med* 2017; 377:923-935



Mean FEV_1 and FVC before and after bronchodilator (top and middle), and the risk of AECOPD over time (bottom)

Mean pre-bronchodilator FEV_1 1.82-1.80 L (73% pred)

Zhou Y, et al. *N Engl J Med* 2017; 377:923-935

Observations

- **FEV_1 with tiotropium was higher than with placebo**
  - 127-169 mLs pre-bronchodilator and 71-133 mLs post-bronchodilator ($p<0.001$ for all comparisons)
- **Post-bronchodilator FEV_1 annual decline significantly less with tiotropium (29 mLs/yr) vs placebo (51 mLs/yr); $p<0.006$**
  - trend to less annual decline of pre-bronchodilator FEV_1: 38 mLs/yr tiotropium vs 53 mLs/yr placebo; $p=0.06$
- **Tiotropium resulted in significantly longer time to 1st AECOPD** (25th%, 522 days; 95% CI 341-649) than placebo (25th%, 236 days; 95% CI, 177-331)
  - **incidence of AECOPD significantly lower with tiotropium than placebo**
- Is this enough evidence to actively diagnosis and treat this patient population?
  - study does address the 'what difference does it make' question

Zhou Y, et al. *N Engl J Med* 2017; 377:923-935

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

Gerard J. Criner[1], Richard Sue[2], Shawn Wright[2], Mark Dransfield[3], Hiram Rivas-Perez[4], Tanya Wiese[4], Frank C. Sciurba[5], Pallav L. Shah[6], Momen M. Wahidi[7], Hugo Goulart de Oliveira[8], Brian Morrissey[9], Paulo F. G. Cardoso[10], Steven Hays[11], Adnan Majid[12], Nicholas Pastis, Jr.[13], Lisa Kopas[14], Mark Vollenweider[15], P. Michael McFadden[16], Michael Machuzak[17], David W. Hsia[18], Arthur Sung[19], Nabil Jarad[20], Malgorzata Kornaszewska[21], Stephen Hazelrigg[22], Ganesh Krishna[23], Brian Armstrong[24], Narinder S. Shargill[25], and Dirk-Jan Slebos[26]; for the LIBERATE Study Group

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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 ΔEBV–SoC of subjects with a post-bronchodilator FEV_1 improvement from baseline of greater than or equal to 15%. Secondary endpoints included absolute changes in post-bronchodilator FEV_1, 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 ΔFEV_1 greater than or equal to 15% ($P <$ 0.001). ΔEBV–SoC at 12 months was statistically and clinically significant: for FEV_1, 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 ΔEBV–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

Criner GJ, et al.
Am J Resp Crit Care Med
2018; 198:1151-1164

Background

- Endobronchial Valves are inserted bronchoscopically to occlude an emphysematous lobe. **Lobar deflation leads to lobar atelectasis, and reduced hyperinflation**
- First RCT (VENT: Endobronchial Valve for Emphysema Palliation Trial) achieved statistical, but not clinically meaningful, improvements in FEV_1 and 6MWD
  - **post-hoc analysis showed only pts with complete fissures in the treated lung and in whom lobar occlusion was achieved had clinically meaningful outcomes**

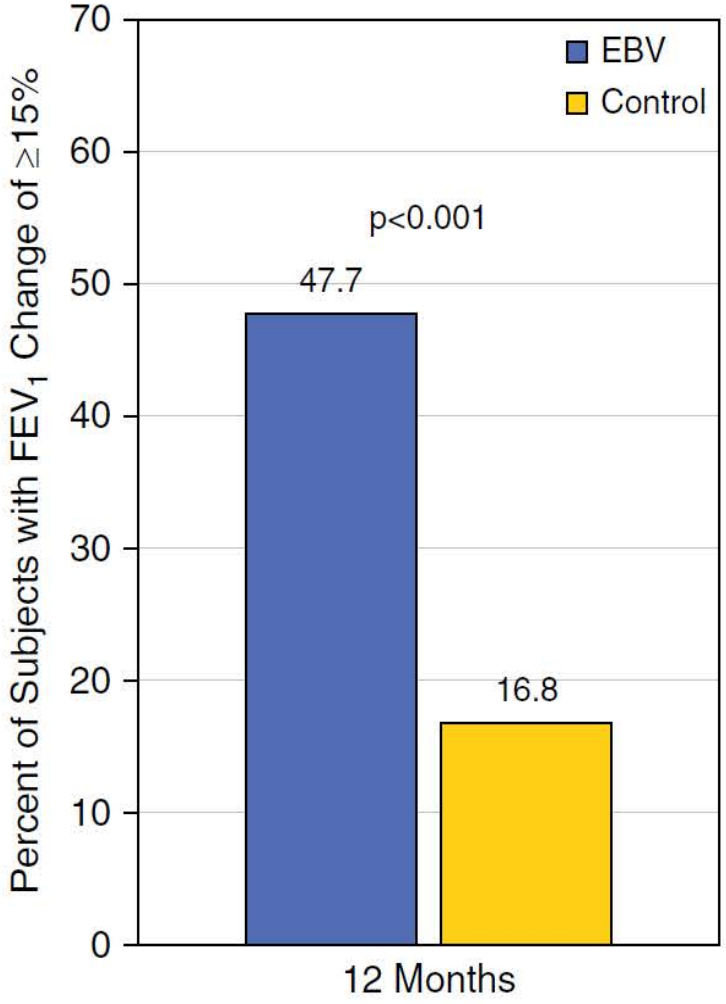
Sciurba FC, et al. *N Engl J Med* 2010; 363:1233–1244. Criner GJ, et al. *Am J Resp Crit Care Med* 2018; 198:1151-1164

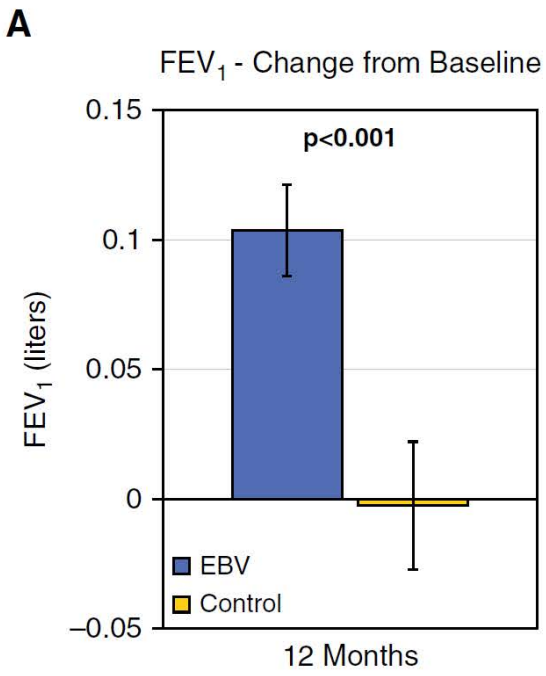
Methods

- n=190, 24 sites, 2:1 randomization (EBV:control)
  - ex-smokers, 40-75 yrs, post-BD FEV_1 15-45% pred, TLC >100% pred, RV ≥175% pred, DLco ≥20% pred, 6MWD 100-500 m after PR program
- Target lobe selection based on >50% destruction score and heterogeneous emphysema (both well defined)
  - **66% LUL, 12% LLL**, 11% RUL, 11% RML/RLL
- Subjects enrolled after bronchoscopy - collateral ventilation assessed with the Chartis Pulmonary Assessment System
  - subjects receiving EBV hospitalized for 5 days
- **1º outcome (12 months) post-bronchodilator FEV_1 ≥15% from baseline**
  - 2º outcomes: absolute change in post-bronchodilator FEV_1, 6MWD, SGRQ

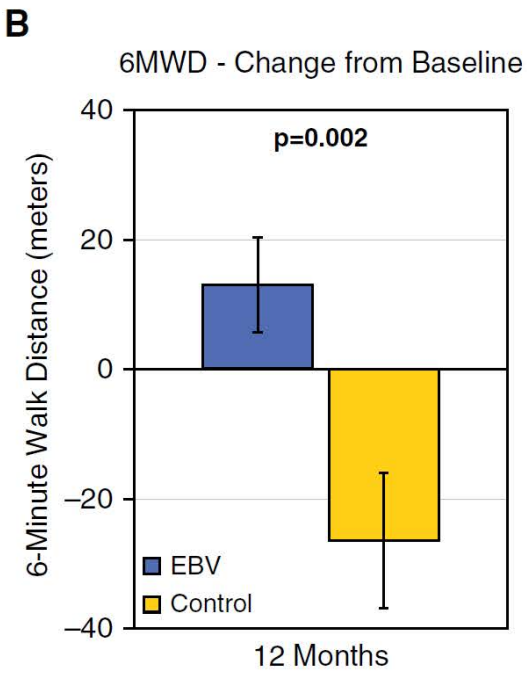
Criner GJ, et al. *Am J Resp Crit Care Med* 2018; 198:1151-1164

Results

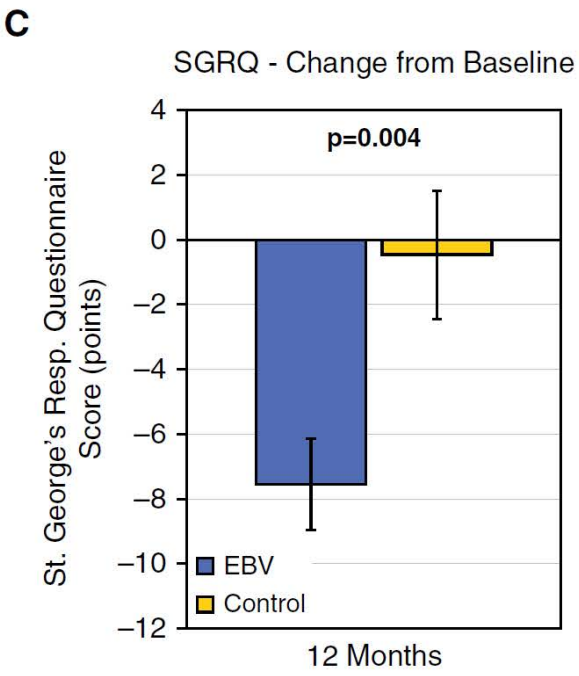




106 mLs



39.3 m



-7.1 u

Criner GJ, et al. *Am J Resp Crit Care Med* 2018; 198:1151-1164

Observations

- **Pneumothorax most common SAE** in treatment period (procedure to 45 d) - 34/128 **(26.6%) of EBV subjects**
  - 35 subjects underwent second procedures
  - 4 deaths in the EBV group during this phase; 1 each in EBV and control between 46 days - 12 months
- Concluded [Zephyr] **EBV clinically improves lung function, exercise, QOL, and dyspnea** (MRC -0.8 u) for at least 12 months, with an acceptable safety profile in pts with little/no collateral ventilation in the target lobe

Criner GJ, et al. *Am J Resp Crit Care Med* 2018; 198:1151-1164

JAMA | Original Investigation

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 ($Paco_2$ >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.

Editorial page 2167

Supplemental content

CME Quiz at jamanetwork.com/learning

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

Murphy PB, et al. *JAMA* 2017; 317:2177-2186

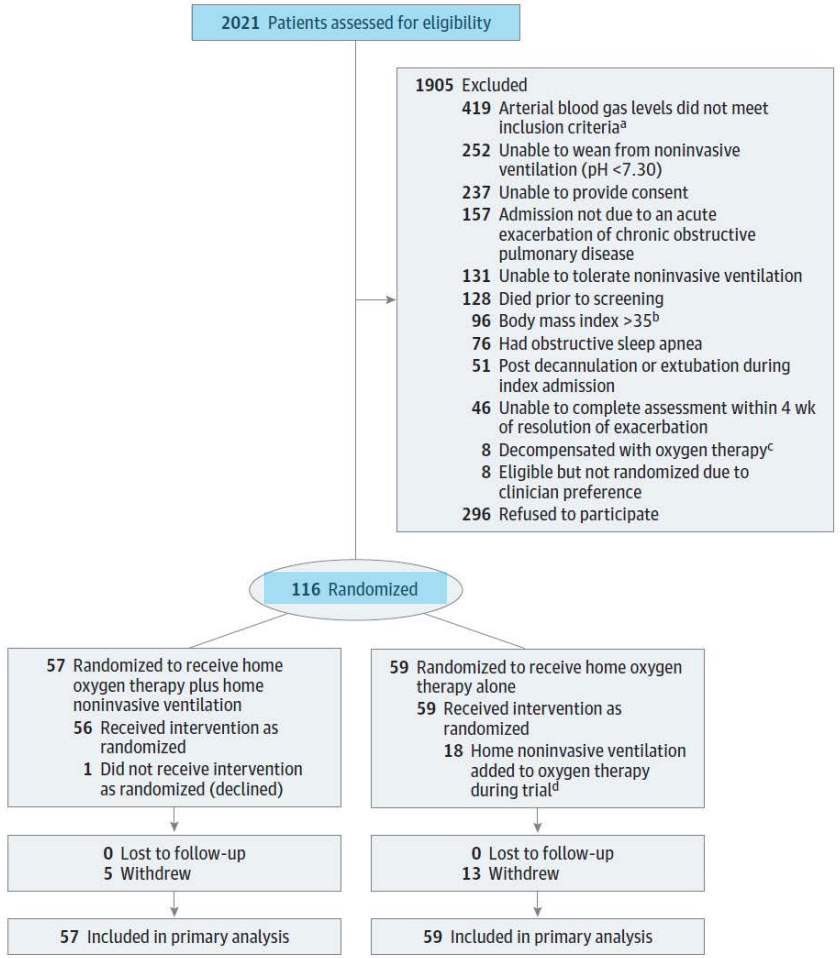
Background

- **NIV has been a 'complete game-changer' in the management of acute severe AECOPD**
  - but outcomes after AECOPD requiring NIV remain poor
- Results from earlier trials exploring home NIV after AECOPD have been mixed, and most recently not supportive of the intervention (no benefit in time to readmission or death, but improved HRQL)[1]
  - **although results with NIV in stable, hypercapnic COPD have been positive** (long-term NPPV, targeted to reduce hypercapnia, improved survival of patients with hypercapnic, stable COPD)[2]
- Examined effect of NIV+ home O_2 vs home O_2

[1]Struik FM, et al. *Thorax* 2014; 69:826-834. [2]Köhnlein T, et al. *Lancet Respir Med* 2014; 2:698-705

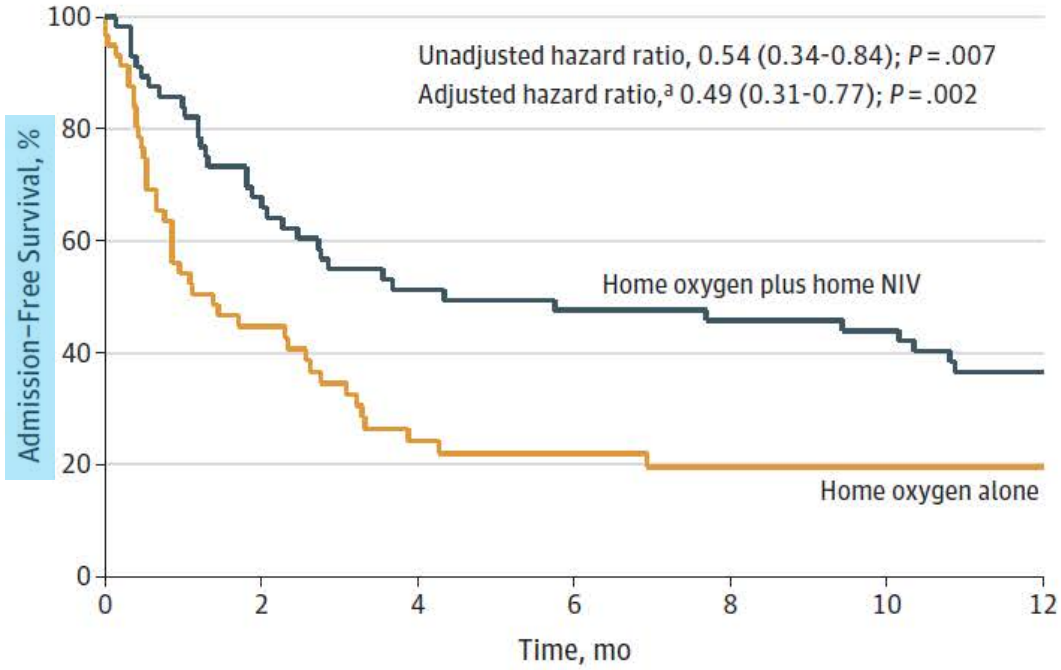
Methods

- Randomized, 13 UK centers, $PaCO_2$ >53 mmHg (2 wks following AECOPD resolution)
  - excluded BMI >35, known OSA
- **Continuous O_2 to maintain PaO_2 ≥60 mmHg**
- NIV begun within 4 wks of discharge with daytime assessment/acclimatization
  - then x 1 yr (**mean 24/4 cmH_2O, backup 14/min**)
- **1^0 endpoint: time to readmission or death within 12 months**, adjusted for number of prior COPD admissions, use of long-term oxygen, age, and BMI



Murphy PB, et al. *JAMA* 2017; 317:2177-2186

Time to Re-Admission or Death



No. at risk

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+O_2 group was **4.3 months** vs **1.4 months** in O_2 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+O_2 group vs 80.4% in the O_2 group (absolute risk reduction **17.0%**; 95%CI 0.1%-34.0%)

Murphy PB, et al. *JAMA* 2017; 317:2177-2186

So What Does This All Mean …?

- **Triple therapy significantly decreases AECOPD vs both ICS/LABA and LABA/LAMA** in mod/severe COPD patients with exacerbations
- **Undiagnosed, symptomatic COPD pts have an increased risk of AECOPD, pneumonia, and death**, while **undiagnosed, asymptomatic COPD pts have an increased risk of AECOPD and pneumonia**
- **Long-acting bronchodilators in pts with mild/moderate COPD significantly improve lung function and decrease AECOPD**
- **Endobronchial valve insertion improves lung function, exercise, QOL, and dyspnea**, for at least 12 months, with an acceptable safety profile, in pts with advanced COPD and little/no collateral ventilation in the target lobe
- Addition of **home NIV to O_2 therapy in stable hypercapnic COPD pts significantly reduces hospital readmission and mortality**