Current Controversies in Chronic Obstructive Pulmonary Disease (COPD), 2018

Gerard J. Criner[1*], Fernando J. Martinez[2], Shawn Aaron[3], Alvar Agusti[4], Antonio Anzueto[5] , Mona Bafadehl[6], Peter J. Barnes [7] , Jean Bourbeau[8], Rongchang Chen[9], Jeffrey Ewig,[10] Leonardo M. Fabbri[11], Peter Frith[12], David M. G. Halpin[13], MeiLan Han, [14] , Maria, Montes deOca [15], Masaharu Nishimura[16], Denis Odonnell, [17] Alberto Papi,[18] Ian Pavord, [19] Nicolas Roche[20], Roberto Rodriguez-Roisin[21], Sundeep Salvi,[22] Dave Singh[23], Don D. Sin[24], Robert Stockley[25], M. Victorina López Varela[26] ,Jørgen Vestbo[27], Claus F. Vogelmeier[28] ; George Washko,[29] Jadwiga A. Wedzicha[30]and Bartolome R. Celli[31]

*These authors contributed equally to the manuscript

[1] Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania, USA; [2] New York-Presbyterian Hospital, Weill Cornell Medical Center, New York, New York, USA; [3] Ottawa Hospital Research Institute, Ottawa CA; [4] Hospital Clínic, Universitat de Barcelona, Ciberes, Barcelona, Spain; [5] University of Texas Health Science Center and South Texas Veterans Health Care System, San Antonio, Texas, USA; [6] Nuffield Department of Medicine, University of Oxford, Oxford, UK; [7] National Heart and Lung Institute, Imperial College, London, United Kingdom; [8] McGill University Health Centre, McGill University, Montreal, Canada; [9] State Key Lab for Respiratory Disease, Guangzhou Institute of Respiratory Disease, First Affiliated Hospital of Guangzhou Medical University, Guangzhou, PRC; [10] Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia PA; [11] University of Modena & Reggio Emilia, Modena, Italy; [12] Flinders University Faculty of Medicine, Bedford Park, South Australia, Australia; [13] Royal Devon & Exeter Hospital, Exeter, UK; [14] University of Michigan, Ann Arbor, MI; [15] Hospital Universitario de Caracas Servicio de Neumonología y Cirugía de Tórax, Caracas, Venezuela; [16] Hokkaido University School of Medicine Sapporo, Japan; [17] Queens University, Ontario, CA, [18] University of Ferrara, Italy,[19]Respiratory Medicine Unit, Nuffield Department of Medicine,Oxford, UK [20] Hôpital Cochin (APHP), University

Paris Descartes, Paris, France; [21] Thorax Institute, Hospital Clinic Universitat de Barcelona, Barcelona, Spain; Sundeep Salvi,[22] ; [23] University of Manchester, Manchester, UK; [24] St. Paul's Hospital, University of British Columbia, Vancouver, Canada; [25] University Hospital, Birmingham, UK; [26] Universidad de la República, Hospital Maciel, Montevideo, Uruguay; [27] Education and Research Centre,University Hospital of South Manchester NHS Foundation Trust; [28] University of Marburg, Marburg, Germany, Member of the German Center for Lung Research (DZL); [29] Brigham and Women's Hospital Boston, Massachusetts, USA; [30] Imperial College London, London, UK; [31] Brigham and Women's Hospital Boston, Massachusetts, USA

Correspondence and reprint requests:

Gerard J. Criner, M.D.
Professor and Chair, Department of Thoracic Medicine and Surgery
Director, Temple Lung Center
Lewis Katz School of Medicine at Temple University
745 Parkinison Pavilion
3401 North Broad Street
Philadelphia PA 19140
Email: gerard.criner@tuhs.temple.edu
Phone (office): 215 707-8113
Phone (cell): 215 510-6570
Fax: 215 707-6867

Running head: Current Controversies in COPD, 2018
Mesh terms: COPD, exacerbation, airflow obstruction
Abstract word count: 202
Body text total word count: 5,380
Key point summary words: 795
Body text excluding key point summaries: 4,564

Abstract

Research demonstrates that Chronic Obstructive Pulmonary Disease (COPD) is not only preventable, but treatable. Despite these efforts, COPD continues to claim many lives, and disable many more, without any cure in sight. Our inability to reverse the devastating course of COPD is in part due to the fact that it is often recognized late, after the disease has advanced. In addition, COPD is a complex disease with protean pulmonary and non-pulmonary manifestations punctuated by episodic escalations of respiratory symptoms in a predominately older patient population with multiple comorbidities.

The major objective of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) is to improve the diagnosis, assessment and prevention of COPD by increasing awareness while simultaneously stimulating new research. GOLD publishes an annual report that provides recommendations, however, it is clear that some major issues regarding COPD management are not certain, and that limited or contradictory data exists in important areas that requires further information to guide recommendations. The GOLD scientific committee recently conducted a public forum where controversial topics were discussed to define the current gaps in knowledge regarding the diagnosis, assessment and treatment of COPD. Herein, we summarize the results of that discussion.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable worldwide leading cause of morbidity and mortality that markedly increases healthcare costs. Smoking cessation, vaccinations, supplemental oxygen for hypoxemic patients and lung volume reduction surgery in selected patients all improve survival; smoking cessation also attenuates disease progression. Several inhaled, oral and systemically administered drugs improve lung function, decrease the frequency and severity of COPD exacerbations and improve patient's quality of life. Pulmonary rehabilitation, noninvasive ventilation and lung volume reduction also improve outcomes in selected patients. Despite these efforts, COPD continues to claim many lives, and disable many more. COPD is a complex process with protean pulmonary and non-pulmonary manifestations punctuated by episodic escalations of respiratory symptoms in a predominately older patient population with multiple comorbid conditions.

Bridging Knowledge gaps in COPD

The GOLD scientific committee conducted a public forum where controversial topics were discussed to define current gaps in our knowledge. These topics included: 1) diagnosis and assessment; 2) risk factors for disease development; 3) advances in treatment of the stable patient and; 4) the assessment and treatment of exacerbations. This manuscript summarizes that discussion and provides information about current research needs.

Diagnosis and Assessment of COPD

Is airflow limitation essential to diagnose and treat COPD?

COPD comprises a complex and heterogeneous group of entities caused by different agents acting through various pathobiological processes. COPD appears to be more a syndrome than a single disease, however, all processes lead to a common physiological endpoint, airflow limitation, measured as the forced expiratory volume expired during the first second (FEV_1). Labeling the disease as "obstructive" distinguishes COPD from other respiratory diseases that cause similar symptoms. Spirometric "obstruction" remains despite administration of inhaled bronchodilators, a feature that differentiates COPD from asthma.

Spirometric determined airflow limitation is required to diagnose COPD. (1) Recent studies reported respiratory symptoms in smokers without obstructed spirometry.(2, 3) Their symptoms were severe enough to impact on their quality of life scores and were associated with exacerbation like events. Thus, the question arises as to whether these subjects suffer from

COPD, and if so, would it be possible to diagnose COPD without the presence of obstructive spirometry? A recent proposal for an updated taxonomy of COPD suggests the term of Pre-COPD for subjects with these characteristics.(4) While these issues remain unsettled, there is agreement that subjects at risk (history of smoking, environmental exposure or family history of respiratory diseases) and those with respiratory symptoms of dyspnea, cough and sputum production are candidates for spirometry to help determine the physiological presence and severity of airflow limitation.

Key points:

The persistence of respiratory symptoms and airflow limitation are key to the diagnosis of COPD. Future work needs to determine the prognosis and response to treatment of at risk individuals who have persistent respiratory symptoms without airflow obstruction.

What symptoms are pivotal in the assessment and treatment of patients with COPD?

The 2017 GOLD Report states that the most common respiratory symptoms are dyspnea, cough and/or sputum production; however, dyspnea on exertion is the most dominant one. (5, 6) Several scales can quantify the severity of symptoms. The modified Medical Research Council (mMRC), Borg, and baseline dyspnea and transitional dyspnea index (BDI/TDI) measure dyspnea. The Saint George's Respiratory Questionnaire (SGRQ), COPD assessment test (CAT), and chronic respiratory questionnaire (CRQ) evaluate overall health status, including dyspnea. (7) The 2017 GOLD Report suggests to base pharmacological treatment on symptom load and exacerbation risk except in cases with a marked discordance between airflow limitation and perceived symptoms. In those cases, a detailed evaluation should be performed with full lung function tests, computed tomography, exercise tests and examination for comorbidities to explain any discordant findings.

Key Points:

Dyspnea on exertion is the most frequently reported symptom, but it is not COPD-specific indicating that other diagnoses need to be considered.

Role of chest imaging in the diagnosis and treatment of COPD

Patients with COPD usually suffer from combinations of emphysema and small airways abnormalities which explains why patients with similar degrees of airflow obstruction have marked differences in symptoms, quality of life and survival. Computed tomographic (CT) imaging provides *in-vivo* assessments of organ structure and suggests that CT imaging coud identify clinically relevant subtypes of COPD with variable treatment responses.

An example of the clinical utility of thoracic imaging in COPD is demonstrated by lung volume reduction surgery (LVRS) evaluation. The National Emphysema Treatment Trial (NETT) compared LVRS vs optimal medical therapy in severe emphysematous COPD patients.(8) While there was no overall benefit from LVRS, a subset of patients with upper zone predominant emphysema on CT scan and low exercise capacity experienced a reduction in symptoms and improved survival after LVRS.

Subjects with normal spirometry can have significant emphysema and gas trapping on expiratory CT scan as well as airway wall thickening and small airways abnormalities.(2, 3) Image based investigations are also exploring the non-pulmonary manifestations of smoking related injury such as osteoporosis, atherosclerosis and metabolic syndrome.

Imaging has broadened our conceptualization of COPD to encompass a spectrum of smoking related conditions including parenchymal inflammation and fibrotic lung disease.(9) In addition, imaging and pathological studies have suggested that small airway injury may be accompanied by inflammatory overspill to the surrounding alveoli leading to remodeling, and centrilobular emphysema.(10-12)

Image based investigations demonstrate that both airway dilation and macrovasculature pruning independently predict worse clinical outcomes.(13-15) These latter findings, including regional changes in microvascular perfusion (16), suggest that pulmonary vascular disease affects parenchymal remodeling.

Key points

Chest CT characterizes the structure of the airways, lung parenchyma and pulmonary vasculature and can phenotype COPD patients. Further research is needed to determine if chest imaging can guide COPD therapies.

Risk factors for the development of COPD

Host factors (Genetic factors and childhood illnesses)

A recent study reported variable lung function trajectories leading to COPD in late adulthood.(17) Approximately half of adults diagnosed with COPD had an accelerated rate of lung function decline, the other half did not. The latter group already had low lung function in early adulthood suggesting that abnormal lung development (in utero and after birth) is a risk factor for COPD in adulthood. (18, 19)

Lung development is highly complex and influenced by multiple genetic and/or in-utero or post-natal environmental factors, including passive smoking, poor nutrition and repeated infections. (20) These factors can compromise development of other organ systems. (21) A recent study showed that 4–13% of the general population had low lung function (FEV_1 <80% predicted) in early adulthood and a higher prevalence and premature incidence of respiratory, cardiovascular, metabolic abnormalities and mortality.(22) Furthermore, there was evidence of trans-generational reproducibility.(22, 23)

Key points:
Childhood disorders, a diagnosis of asthma, repeated airway infections, and host factors (premature birth, prenatal and perinatal circumstances) can impair lung development that may contribute to COPD in the adult.

Biomass Exposure vs. active and passive cigarette smoking

Smoking is the greatest contributor to COPD burden in countries with a higher socio-demographic development index (SDI); environmental (biomass exposure) and occupational risks predominate in low-middle or low SDI countries.

Approximately 50% of households worldwide (3 billion people) and 90% of rural households in low income countries use biomass fuel as their main domestic energy source.(24) In low SDI quintile countries, women, young girls, and children have long biomass exposure. In China, mortality due to COPD caused by biomass smoke exposure is similar to mortality due to tobacco smoking.(25) Exposure to biomass fumes increases the odds of COPD by 2.3-fold. This

is similar to cigarette smoking (OR, 2.12-3.77) (26) and higher than that reported from second hand smoke exposure (OR, 1.48).(27) Combined tobacco smoking and biomass smoke exposure has an OR of 4.39 [3.4-5.7] versus 2.55 [2.0-3.1] for biomass smoke alone*.(28)* Increased ventilation, improved stove design and low-emission fuel use can decrease or prevent biomass exposures. Smoking bans increase quit rates and reduce harm from second-hand smoke exposure. (29)

Exposures to cigarette and biomass smoke cause different COPD phenotypes. Women with COPD from tobacco exposure have more emphysema than those exposed to biomass fumes who have more air trapping and less respiratory symptoms. (30, 31)

***Key points*:**
Besides cigarette smoking, environmental factors (i.e., biomass fuel, poor air quality and occupational exposures) contribute to COPD development. The following needs to be determined: the extent of exposure required to initiate and perpetuate lung disease progression, the differences between COPD induced by cigarette smoking vs biomass exposure, and the best preventative measures that improve clinical outcomes.

Risk factors for the development of COPD: childhood and adolescent asthma

Increased knowledge about the risk factors leading to different lung function trajectories may prompt preventative strategies. Several lung function cohort studies report that lung function "tracks" throughout life and that patients with persistent wheeze and a diagnosis of asthma have diminished lung function that becomes evident in early adulthood. (32-35) Other early life factors associated with lower FEV_1 in adulthood included maternal, paternal, and childhood asthma, severe childhood respiratory infection, and maternal smoking. (36) These "Childhood Disadvantage Factors" were associated with decline in FEV_1 similar to smoking 10–20 cigarettes per day.

The Childhood Asthma Management Program (CAMP) reported that in children recruited (ages 5 and 12 years), 75% had abnormal lung growth patterns: normal growth/early decline (26%); reduced growth only (23%); reduced growth/early decline (26%). (37) Risk factors for abnormal growth and decline were lower lung function at enrollment and male sex. Eleven percent of patients in this cohort met GOLD criteria for COPD, particularly those with a reduced lung

growth pattern. Data from the Tucson Children's Respiratory Study showed that approximately 10% of their subjects had a low lung function trajectory. (19) These subjects had a higher incidence of active asthma, mothers with asthma, lower lung function in infancy, and RSV infections in early life. (38, 39)

Key points:

Airway abnormalities that occur early in life and/or the diagnosis of childhood asthma, may precipitate a lower trajectory of lung function that increases the risk of developing COPD in the adult.

Impact of gender on COPD development

COPD prevalence is increasing more rapidly in women than men. (40) In some countries, female COPD-related deaths now surpass men. Gender encompasses not just differences in disease biology but also differences in environmental exposures and psychosocial factors that affect disease development. Females achieve peak lung function earlier than males (15 vs. 22 years). Yet, both start smoking at the same age, suggesting that the impact of smoking in a mature (females) or immature (males) lung may be different. (41)

Women are more susceptible than men to develop COPD with tobacco exposure.(42) A meta-analysis of studies examining the annual decline in FEV_1% predicted in smokers, observed significantly faster annual lung function declines in women than men.(43) Women are over-represented in the subset of COPD patients with severe disease despite lower tobacco smoke exposure (< 20 pack years) and also in patients under the age of 60.(44) Female ex-smokers are at increased risk for airflow obstruction after 10 pack-years exposure as compared to 19 pack-years for men (Figure 1).(45)

Potential causes of sex differences in tobacco susceptibility include differences in metabolism, hormonal influences, lung anatomy, inhalation technique, or a dose expossure since females' lungs are smaller than males.

Sex differences are also apparent in non-tobacco related COPD. Women comprise the majority of patients with COPD who have never smoked; possibly because women have greater biomass exposure through cooking and domestic responsibilities. Less than 1% of women in India smoke yet, non-smokers constitute 65% of all female patients who meet spirometric criteria for COPD. Women exposed to biomass fuel during childhood have greater risk for

COPD than those exposed later (OR 2.9 vs 1.3). The Canadian chronic obstructive lung disease (CanCOLD) study demonstrated that exposures to passive smoke and biomass fuels was an independent risk factor for women to develop COPD.(46)

Sex may influence the response to smoking cessation therapies. In the Lung Health Study (LHS) women who became sustained quitters had 2.3 times greater improvement in lung function compared to men.(47) The LHS also demonstrated that fewer women were able to achieve smoking cessation. A large, national community study in Canada suggests women who smoke have higher nicotine addiction levels than their male counterparts.(48)

Women, may also differ in response to other therapies. Pooled analyses of indacaterol/glycopyrronium studies reported greater quality of life improvements in women versus men.(49)

Key points:

COPD prevalence is increasing more rapidly in women than men. In some countries female COPD-related deaths surpass those in men. Women are more susceptible to tobacco smoke and may have greater lung function improvement with smoking cessation than men. More research is needed to determine the impact of gender on these issues.

Aging and COPD

Theories of aging fall into two main categories: programmed and damage theories.(50) Programmed theories implies aging follows a biological timetable, similar to processes that regulate childhood growth and development. In contrast, damage theories emphasize aging derives from environmental assaults inducing injury and cellular and molecular DNA damage. COPD fits well with damage theories of aging since cigarette smoke, noxious fumes and dusts, increase oxidative stress that cause DNA damage.

The prevalence of COPD increases with age, from 3.2% among those aged 18–44 years to 11.6% among those aged ≥ 65 years, increasing two-fold for every 10-year increment above age 40. The diagnosis of COPD in the elderly can be difficult since some patients are unable to perform adequate spirometry. In the SARA study only 78% of elderly subjects (> 65 years) could perform reproducible spirometry. (51)

The amount of used medications coupled with cognitive dysfunction impacts adherence. Scoring less than 24 on the Mini-Mental State Examination carries a very high risk of inhaler device failure. (52) Age and gender are more important determinants of inspiratory flow through dry powder inhalers (DPIs) than the degree of airway obstruction. (53)

Elderly COPD patients are more prone to drug side effects including: an increased risk for pneumonia with the use of ICS, urinary obstruction with inhaled anticholinergics, theophylline toxicity due to reduced metabolism despite therapeutic levels.

Polypharmacy is common in the elderly. A population study of 191,005 elderly COPD patients > 66 years old in Canada found that newly prescribed long-acting inhaled β-agonists and anticholinergics had a higher risk of hospitalization or ED visit for a cardiovascular event compared with non-use of those medications. (54)

Key points:
COPD may be considered a disease of accelerated aging that disproportionately afflicts the elderly. Current PFT reference standards may over diagnose airflow obstruction in the elderly. COPD disproportionately impacts the elderly due to more comorbid conditions, impaired cognition and difficulties with proper inhaled therapy. More research is needed to understand the impact of COPD in the elderly.

Treatment of COPD

Is personalized treatment a viable goal?

Phenotyping patients with COPD advances an understanding of the pathogenesis of COPD and the risks and benefits of various therapies. Multiple large observational trials have enhanced the phenotyping of the COPD population. ECLIPSE, BODE, COPDGENE, CanCOLD and SPIROMICS are efforts to explore the unique features of COPD and the demographic, physiological and radiological features that better characterize COPD sub-groups. (55-59)

Symptom burden and smoking status regardless of the presence or degree of airflow obstruction, affects the response to inhaled therapies.(60) The degree of hypoxemia influences the response to chronic supplemental oxygen and the persistence of significant hypercapnia

signals the response to noninvasive ventilation.(1) Physiological characterization of hyperinflation coupled with the presence of intact fissures differentiates patients' responses to bronchoscopic lung reduction.(61, 62) Absolute number and % of blood eosinophils, predicts exacerbation risk, and the response to systemic and inhaled corticosteroids and anti-L-5 antagonists.(63-66) New tests that assess biological mechanisms (e.g. endotypes) may identify the presence of treatable traits regardless of the clinical labeling of the disease (e.g., asthma vs COPD) and foster the use of precision medicine in treating patients with COPD.(67)

These data suggest that phenotypic characterization of COPD patients is critically important to assess the subsets of patients with COPD more likely to respond to a therapy and better balance clinical benefit over risk.

Key points:

Phenotypic characterization of patients with COPD has implications for the approach to selected treatments. Research is needed to discover tools that can enhance phenotypic characterization, especially in the area of blood biomarkers for the diagnosis, prognosis and response to therapy*.*

Maximal bronchodilation at initiation of therapy vs progressive bronchodilation?

Inhaled bronchodilators improve lung function, activity-related dyspnea, exercise tolerance and perceived health status. (1) Bronchodilator choices should be individualized and based on assessment of physiological impairment, symptom burden, and exacerbation risk. These three factors, together with drug safety, cost and patients' preference for device and medication, helps clinicians chose the best treatment for an individual patient. The question arises what is best?: 1) progressive escalation of bronchodilator therapy or 2) "maximizing" bronchodilator therapy with dual bronchodilator therapy, ab initio. The rationale for the latter is that optimal, sustained, reversal of abnormal respiratory mechanics is best achieved by combining bronchodilator classes that work on different pathways: long-acting anti-muscarinic (LAMA) and Beta-2 agonist (LABA). Conversely, does the onset of dual bronchodilator therapy substantially increase the risk of side effects compared to use of a single agent?

It seems reasonable that in patients with significant symptom burden, effective sustained 24-hour bronchodilation and lung deflation should be the primary goal. Two recent meta-analyses of seven studies (68, 69) show that dual LAMA/LABA FDC provide significantly greater

improvements in spirometry, lung hyperinflation, activity-related dyspnea, exercise tolerance, and health-related quality of life than the constituent monocomponents. In many patients, respiratory mechanics progressively worsen during sleep, therefore effective night-time bronchodilation should help alleviate evening and early morning symptoms. (70) (71) Dual LABA/LAMA FDC prescribed twice daily can achieve superior nocturnal and early morning bronchodilation than LAMA alone.(70, 72) (60)

The choice of bronchodilator initiation therapy ("maximal" or progressive) in less severely affected patients is more problematic given the paucity of clinical trials in this sub-population. However, many patients under-report their symptoms of exertional dyspnea because of successful temporal adaptation to their insidious disability and habitual avoidance of physical activity. These patients can have impaired pulmonary gas exchange and significant resting and exercise lung hyperinflation. Given that lung hyperinflation is linked to increased mortality and risk of severe exacerbations, initiation of dual FDC treatment may be a reasonable first choice for these patients.

If a single agent is chosen, evidence supports using a LAMA (tiotropium) since it improves lung function (including FEV_1 decline) and quality of life scores even in patients with mild COPD with minimal symptoms. (73)

Key points: Dual bronchodilators improve symptoms, increase physical activity, slow disease progression, reduce exacerbations and provide effective sustained 24-hour bronchodilation and lung deflation. More research is needed to determine the patient profile and disease stage where long acting bronchodilators and their combinations should be initiated and maintained to maximize patient outcome.

What is the role of inhaled corticosteroids (ICS) in the therapy of COPD?

The sole use of ICS to treat patients with COPD is discouraged because of its limited effect on lung function, potential for side effects and association with increased mortality in the TORCH trial when compared with an ICS/LABA combination. However, when ICS is combined with LABA in patients with a history of prior exacerbations, or concomitant asthma and COPD, there

is a consistent effect on exacerbation reduction. Combined ICS/LABA is more effective than the individual components in improving lung function, health status and reducing exacerbations (74, 75)

Patients with moderate and severe COPD are commonly treated with “triple therapy”, either combination ICS/LABA and a long-active anticholinergic (LAMA) or newly approved triple combinations in a single inhaler because they improve symptoms, lung function(76), quality of life, and reduce exacerbation frequency with a potential improvement in survival.(66, 76, 77), particularly when compared to LAMA (77) or LABA/LAMA combinations. (66, 78)

ICS have side-effects such as pneumonia, skin thinning and bruising, bone fractures (79) and oropharyngeal candidiasis. (80) In a meta-analysis of randomized controlled trials, the risk of pneumonia increased in patients receiving ICS at doses > 1000 µg of beclomethasone equivalent/day (OR 1.56, [1.30 to 1.86]) (81). This excess risk has also been confirmed using fluticasone furoate, even at lower doses. Immune suppression may be involved to link ICS use with the increased risk of tuberculosis and non-tuberculous mycobacterial disease. (82)

Switching patients at low risk of COPD exacerbations from LABA+ICS to LABA alone did not affect symptoms or health status or COPD exacerbation rates over 1 year. (83) A systematic review found no evidence that withdrawing ICS results in a deterioration in outcomes (84), other than a modest decrease in FEV_1 (of the order 40 mL). (85, 86)

Key points:

ICS have been predominately used in COPD patients as combination therapy (with LABA or LABA/LAMA) for exacerbation prevention. Although combinations of ICS with long acting bronchodilators have reduced exacerbation frequency and severity and improved quality of life and lung function, its effect on mortality remains unclear. Ongoing and recently completed studies evaluating the impact of ICS combined with LABA or LABA/LAMA will hopefully expand our knowledge about the risks and benefits of ICS use in patients with COPD. (66, 77, 78, 87)

Peripheral eosinophils are a useful biomarker in COPD

Some COPD patients have eosinophilic airway inflammation when stable (88) and during exacerbations. (89) Sampling the airways is time-consuming, and the potential of blood eosinophils as a more practical COPD biomarker has been investigated. A population study showed that patients with eosinophil counts >340 cells/μL had increased exacerbations .(90) However, two long-term cohort studies (91, 92) found no increased risk of moderate-severe exacerbations when a threshold of ≥2% blood eosinophils was used. (90) Analyses of the COPDgene and ECLIPSE cohorts showed increased risk of exacerbations in patients with >300 eosinophils/μL, primarily driven by the subgroup with ≥2 exacerbations in the prior year. While blood eosinophil counts have utility to predict exacerbations in high risk patients, diverse results are reported from studies with patients at low risk or on an CS. While some studies show that increased blood eosinophils are associated with better lung function, quality of life (93) and reduced mortality (92, 94), these findings are not consistent. In contrast, eosinopenia (count $<0.05 \times 10^9$/L) is associated with sepsis (95), worse outcomes in patients hospitalized with exacerbation (96, 97), and increased pneumonia risk. (63)

Several post-hoc and pre-specified analyses of clinical trials report that the effects of ICS on exacerbations can be predicted by blood eosinophil counts, either for ICS/LABA vs. LABA (64, 98) or triple therapy vs. LABA/LAMA (77, 78, 87). A pooled analysis (n=4528) showed that ICS benefits were observed at >100 eosinophils/μL with greater effects seen at higher eosinophil levels.(99) These analyses suggest that a low eosinophil threshold (such as <100 eosinophils/μL) may be a negative predictor of ICS effects, while a higher threshold (such as >300 eosinophils/μL) suggests that ICS will be beneficial. A post-hoc analysis of two studies (100) (101) supports this statement. Addtiionally, trials with mepolizumab (anti-IL-5) reported that exacerbation reduction (63) was greatest in patients with eosinophil counts >300 cells/mm^3.

There have been concerns regarding the reproducibility of blood eosinophils in COPD patients. (102) While there can be considerable variability at higher levels (e.g. >300 eosinophils/μL), (92) (102) the reproducibility at lower levels appears acceptable. (103)

Key points:

There is evolving evidence that blood eosinophil levels may be associated with important outcomes in patients with COPD. Although the eosinophil has promise as a biomarker in patients with COPD, more work conducted within prospective and controlled trials is

needed to understand the role and practical value of measuring eosinophils in patients with COPD.

Exacerbations of COPD

A new definition of COPD exacerbations is needed?

The first definition of COPD exacerbation focused exclusively on three cardinal symptoms, " worsening of shortness of breath, sputum production and/or sputum purulence." (104) Eleven years later, an event-driven definition was introduced, "a worsening of COPD symptoms requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids, and other bronchodilator therapy, with the aim to assess the efficacy of ICS to prevent COPD exacerbations". (105) A subsequent consensus conference defined exacerbation as "an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and necessitates a change in regular medication, in a patient with underlying COPD." (106) The definition was later refined as: "may warrant a change in regular medication" to acknowledge that exacerbations often go unreported (107).

The consensus definition is the most quoted definition because it integrates the *clinical worsening of an acute event* with *a change in the regular treatment for COPD*. It also grades mild to severe conditions based on management and prompts consideration for other events that mimic an acute exacerbation. These events may be pulmonary (i.e., pneumonia, pulmonary thromboembolism) or cardiac in nature, (i.e., congestive heart failure, arrhythmias). (108)

A recent study (109) used multi-level network analysis to investigate pathobiological mechanisms of exacerbations and biomarkers. The main findings were: (1) exacerbations represent a disruption of the network observed during convalescence, indicating less resilience and homeokinesis during exacerbations; and, (2) a panel of biomarkers (i.e., increased levels of dyspnea, circulating neutrophils and C-reactive protein (CRP)) has a high predictive value for the diagnosis (AUC 0.97). These hypotheses needs to be explored in future studies. (110)

Key points:
Current definitions of exacerbations of COPD are limited by the subjective and variable nature of symptoms defining their occurrence. The lack of an objective biomarker that

indicates the onset and severity of an exacerbation is a major limitation . An easy to use objective definition of exacerbation that incorporates symptom change with biomarker characterization is needed.

Determining the cause of exacerbations: does it matter?

COPD exacerbations increase hospitalizations, impair quality of life, worsen lung function and increase mortality. Most exacerbations are attributed to respiratory infections (50-70%), including bacteria, atypical organisms and respiratory viruses.(111) Except for influenza, there is no specific anti-viral treatment. Viral infections may also precipitate secondary bacterial infections.(112) Many patients require antibiotics and systemic corticosteroids to treat an acute exacerbation. A systematic review of placebo-controlled studies shows that antibiotics reduce short-term mortality by 77%, treatment failure by 53% and sputum purulence by 44% during acute exacerbations. (113) Another systematic review of placebo-controlled studies reports that systemic corticosteroids reduce the risk of treatment failure by 50% but increase side effects by 200%. (114)

Biomarkers have been used to phenotype exacerbations. Levels of C resctive protein (CRP) demonstrate contradictory findings and are often elevated in both bacterial and viral infections. A recent meta-analysis reports that procalcitonin-based protocols (indicative of bacterial infections) can decrease antibiotic prescription (RR 0.56, 95% CI 0.43–0.73) without adversely affecting clinical outcomes.(115) Whether procalcitonin based protocols are cost effective or improve outcomes remains unknown.

COPD exacerbations must be differentiated from other conditions like myocardial infarction, CHF, pulmonary embolism, and pneumonia which may present similarly. However, therapeutic options remain limited beyond antibiotics and systemic corticosteroids.

Key points:

The cause of a COPD exacerbation is needed to institute appropriate treatment. Current treatment of acute exacerbations is limited to administration of short acting bronchodilators, glucocorticoids and antibiotics. Novel, more effective agents are needed to treat the infectious, inflammatory and oxidative stress states that occur during an acute exacerbation.

Exacerbations can be totally prevented?

The GOLD 2017 Report lists interventions other than inhaled medications that can reduce the frequency of exacerbations (1)

Chronic macrolide use has been recommended for some COPD patients. Among selected subjects, azithromycin taken daily for one year decreases exacerbation frequency by 27%, but causes hearing loss and induces changes in microbial resistance patterns. (116) Accordingly, reduction in the frequency of azithromycin use has been suggested (e.g., 3 times weekly), and monitoring of macrolide resistance is warranted.

Roflumilast can decrease exacerbations in patients who have severe COPD whether on ICS, bronchodilators, or both. (117, 118) These benefits were primarily in patients with cough and sputum production. Although its side effects are important (nausea, vomiting and weight loss), it has a role in selected patients.

Mucoregulators have been studied in COPD. The frequency of COPD exacerbations with a high dose of oral N-acetylcysteine (NAC) was lower than placebo during the year of study (119); similarly, NAC treatment was more effective in GOLD-2 than in GOLD-3 patients (120). Carbocisteine induced a 25% reduction in exacerbations. (121) However, due to heterogeneity in the studied populations, these results were unable to identify a target population.

Low-dose theophylline has potential anti-inflammatory benefits that may help prevent exacerbations. (122) Low-dose slow-release theophylline (100 mg, b.i.d.) in a randomized trial significantly delayed the time to the first exacerbation, however in another trial, theophylline on top of LABA+ICS did not impact exacerbation rate. (123) Because of side effects, theophylline remains a 4th line drug for exacerbation prevention.

Key points:
Inhaled and oral agents can prevent exacerbations. However, none of these agents are potent enough to totally eradicate exacerbations. Because even one exacerbation in a fragile patient can be life threatening, future research must identify more effective treatments.

Treatment of exacerbations is currently adequate?

Short acting bronchodilators, such as inhaled $beta_2$-agonists and short-acting anticholinergics, are the initial bronchodilators for acute treatment of COPD exacerbation. A systematic review of the route of delivery of short-acting bronchodilators found no significant differences in FEV_1 between using metered dose inhalers (MDI) (with or without a spacer device) or nebulizers to deliver the agent.(124) Studies have shown that systemic glucocorticoids in COPD exacerbations improve lung function (FEV_1), decrease early relapse, treatment failure and hospitalization duration. (125) (126) (127)Whereas older studies used larger doses of corticosteroids, recent studies report that a lower dose for 5 days may be sufficient.(128) Oral steroid therapy is equally effective to intravenous administration. (129)

A systematic review of the placebo-controlled studies reported that antibiotics reduce the risk of short-term mortality, treatment failure, and prolonged the interval between exacerbations. (113, 130) Antibiotic choice should be based on local bacterial resistance pattern; initial empirical treatment is usually an aminopenicillin with or without clavulanic acid, macrolide, or tetracycline. Route of administration (oral or intravenous) depends on swallowing function and pharmacokinetics of the antibiotic. The recommended length of antibiotic therapy is 5-7 days.

A major impediment to improving outcomes in exacerbation is that the pharmacological treatment has not substantially changed over the last 4 decades.

Key points:

Treatment of COPD exacerbation has not substantially changed over the past several decades. Objective biomarkers that capture the totality of the event from a mechanistic level (inflammatory and injury) is needed.

Is non-pulmonary treatment useful in the prevention of acute exacerbations ?

Although the lung is the primary target organ, smoking affects other organs due to generalized injury (131-133). It is possible that changes caused by COPD per se (such as hypoxemia, chronic systemic inflammation, increased oxidative stress levels and hyperinflation) contribute to the progression of non-pulmonary organ injury.

Management of patients with COPD must include identification and treatment of other concomitant diseases. The presence of comorbidities should not alter COPD treatment, and concomitant diseases should be treated according to single disease guidelines regardless of COPD. Simplicity of treatment and avoidance of gross polypharmacy should be ensured.

Non-pulmonary diseases that afflict COPD patients includes cardiovascular, peripheral vascular disease, bronchiectasis, asthma, sleep apnea, interstitial lung diseases, pulmonary hypertension, obesity, diabetes, osteoporosis, GERD, chronic liver disease, anemia and renal failure. Of particular importance are congestive heart failure, atrial fibrillation, coronary artery disease, depression, anxiety and lung cancer, all occur more frequently in patients with COPD than those without COPD. Their presence significantly increases the risk of death.(134)

In patients hospitalized for COPD, pulmonary rehabilitation post hospitalization may prevent re-hospitalization and even reduce mortality.

Key points:
Comorbidities are common in patients with COPD and can mimic the symptoms of an acute exacerbation. Comorbid conditions are difficult to discover at times and high vigilance is needed to detect and treat them optimally. Post hospitalization rehabilitation improves outcomes and needs to be more accessible.

Summary

Although much progress has been made over the past several decades with the diagnosis, assessment and treatment of patients with COPD, many questions remain unanswered. The issues discussed above outline areas that require active research to discover new characterization tools, biological targets and better preventive and therapeutic measures. Particular attention should be given to events in early life to avoid developmental impairment that results in chronic airflow obstruction in adulthood. Concerted multidisciplinary efforts by academia, clinicians, pharma companies, society and patients are needed to help slow the high worldwide burden of COPD.

References

1. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, Chen R, Decramer M, Fabbri LM, Frith P, Halpin DM, López Varela MV, Nishimura M, Roche N, Rodriguez-Roisin R, Sin DD, Singh D, Stockley R, Vestbo J, Wedzicha JA, Agustí A. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. *Am J Respir Crit Care Med* 2017; 195: 557-582.
2. Regan EA, Lynch DA, Curran-Everett D, Curtis JL, Austin JH, Grenier PA, Kauczor HU, Bailey WC, DeMeo DL, Casaburi RH, Friedman P, Van Beek EJ, Hokanson JE, Bowler RP, Beaty TH, Washko GR, Han MK, Kim V, Kim SS, Yagihashi K, Washington L, McEvoy CE, Tanner C, Mannino DM, Make BJ, Silverman EK, Crapo JD, Genetic Epidemiology of CI. Clinical and Radiologic Disease in Smokers With Normal Spirometry. *JAMA Intern Med* 2015; 175: 1539-1549.
3. Woodruff PG, Barr RG, Bleecker E, Christenson SA, Couper D, Curtis JL, Gouskova NA, Hansel NN, Hoffman EA, Kanner RE, Kleerup E, Lazarus SC, Martinez FJ, Paine R, 3rd, Rennard S, Tashkin DP, Han MK, Group SR. Clinical Significance of Symptoms in Smokers with Preserved Pulmonary Function. *N Engl J Med* 2016; 374: 1811-1821.
4. Celli BR, Agusti A. COPD: time to improve its taxonomy? *ERJ Open Res* 2018; 4.
5. Han MK, Muellerova H, Curran-Everett D, Dransfield MT, Washko GR, Regan EA, Bowler RP, Beaty TH, Hokanson JE, Lynch DA, Jones PW, Anzueto A, Martinez FJ, Crapo JD, Silverman EK, Make BJ. GOLD 2011 disease severity classification in COPDGene: a prospective cohort study. *Lancet Respir Med* 2013; 1: 43-50.
6. Kim V, Crapo J, Zhao H, Jones PW, Silverman EK, Comellas A, Make BJ, Criner GJ, Investigators C. Comparison between an alternative and the classic definition of chronic bronchitis in COPDGene. *Ann Am Thorac Soc* 2015; 12: 332-339.
7. Glaab T, Vogelmeier C, Buhl R. Outcome measures in chronic obstructive pulmonary disease (COPD): strengths and limitations. *Respir Res* 2010; 11: 79.
8. Fishman A, Martinez F, Naunheim K, Piantadosi S, Wise R, Ries A, Weinmann G, Wood DE, National Emphysema Treatment Trial Research G. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003; 348: 2059-2073.
9. Washko GR, Lynch DA, Matsuoka S, Ross JC, Umeoka S, Diaz A, Sciurba FC, Hunninghake GM, San Jose Estepar R, Silverman EK, Rosas IO, Hatabu H. Identification of early interstitial lung disease in smokers from the COPDGene Study. *Acad Radiol* 2010; 17: 48-53.
10. Diaz AA, Bartholmai B, San Jose Estepar R, Ross J, Matsuoka S, Yamashiro T, Hatabu H, Reilly JJ, Silverman EK, Washko GR. Relationship of emphysema and airway disease assessed by CT to exercise capacity in COPD. *Respir Med* 2010; 104: 1145-1151.
11. Bhatt SP, Soler X, Wang X, Murray S, Anzueto AR, Beaty TH, Boriek AM, Casaburi R, Criner GJ, Diaz AA, Dransfield MT, Curran-Everett D, Galbán CJ, Hoffman EA, Hogg JC, Kazerooni EA, Kim V, Kinney GL, Lagstein A, Lynch DA, Make BJ, Martinez FJ, Ramsdell JW, Reddy R, Ross BD, Rossiter HB, Steiner RM, Strand MJ, van Beek EJ, Wan ES, Washko GR, Wells

JM, Wendt CH, Wise RA, Silverman EK, Crapo JD, Bowler RP, Han MK, Investigators C. Association between Functional Small Airway Disease and FEV1 Decline in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2016; 194: 178-184.
12. Kirby M, Tanabe N, Tan WC, Zhou G, Obeidat M, Hague CJ, Leipsic J, Bourbeau J, Sin DD, Hogg JC, Coxson HO, Can CCRG, Canadian Respiratory Research N, CanCold Collaborative Research Group tCRRN. Total Airway Count on Computed Tomography and the Risk of Chronic Obstructive Pulmonary Disease Progression. Findings from a Population-based Study. *Am J Respir Crit Care Med* 2018; 197: 56-65.
13. Patel IS, Vlahos I, Wilkinson TM, Lloyd-Owen SJ, Donaldson GC, Wilks M, Reznek RH, Wedzicha JA. Bronchiectasis, exacerbation indices, and inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; 170: 400-407.
14. Martinez-Garcia MA, de la Rosa Carrillo D, Soler-Cataluna JJ, Donat-Sanz Y, Serra PC, Lerma MA, Ballestin J, Sanchez IV, Selma Ferrer MJ, Dalfo AR, Valdecillos MB. Prognostic value of bronchiectasis in patients with moderate-to-severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013; 187: 823-831.
15. Estepar RS, Kinney GL, Black-Shinn JL, Bowler RP, Kindlmann GL, Ross JC, Kikinis R, Han MK, Come CE, Diaz AA, Cho MH, Hersh CP, Schroeder JD, Reilly JJ, Lynch DA, Crapo JD, Wells JM, Dransfield MT, Hokanson JE, Washko GR, Study CO. Computed tomographic measures of pulmonary vascular morphology in smokers and their clinical implications. *Am J Respir Crit Care Med* 2013; 188: 231-239.
16. Iyer KS, Newell JD, Jr., Jin D, Fuld MK, Saha PK, Hansdottir S, Hoffman EA. Quantitative Dual-Energy Computed Tomography Supports a Vascular Etiology of Smoking-induced Inflammatory Lung Disease. *Am J Respir Crit Care Med* 2016; 193: 652-661.
17. Lange P, Celli B, Agustí A, Boje Jensen G, Divo M, Faner R, Guerra S, Marott JL, Martinez FD, Martinez-Camblor P, Meek P, Owen CA, Petersen H, Pinto-Plata V, Schnohr P, Sood A, Soriano JB, Tesfaigzi Y, Vestbo J. Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2015; 373: 111-122.
18. Bolton CE, Bush A, Hurst JR, Kotecha S, McGarvey L. Lung consequences in adults born prematurely. *Thorax* 2015; 70: 574-580.
19. Berry CE, Billheimer D, Jenkins IC, Lu ZJ, Stern DA, Gerald LB, Carr TF, Guerra S, Morgan WJ, Wright AL, Martinez FD. A Distinct Low Lung Function Trajectory from Childhood to the Fourth Decade of Life. *Am J Respir Crit Care Med* 2016; 194: 607-612.
20. Martinez FD. Early-Life Origins of Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2016; 375: 871-878.
21. Barker DJ, Godfrey KM, Fall C, Osmond C, Winter PD, Shaheen SO. Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. *BMJ* 1991; 303: 671-675.
22. Agustí A, Noell G, Brugada J, Faner R. Lung function in early adulthood and health in later life: a transgenerational cohort analysis. *Lancet Respir Med* 2017; 5: 935-945.
23. Taylor-Robinson DC, Stanojevic S. Low lung function in early adulthood: morbidity and death. *Lancet Respir Med* 2017; 5: 910-911.
24. Bruce N, Perez-Padilla R, Albalak R. Indoor air pollution in developing countries: a major environmental and public health challenge. *Bull World Health Organ* 2000; 78: 1078-1092.

25. Lin HH, Murray M, Cohen T, Colijn C, Ezzati M. Effects of smoking and solid-fuel use on COPD, lung cancer, and tuberculosis in China: a time-based, multiple risk factor, modelling study. *Lancet* 2008; 372: 1473-1483.
26. Lindberg A, Jonsson AC, Rönmark E, Lundgren R, Larsson LG, Lundbäck B. Prevalence of chronic obstructive pulmonary disease according to BTS, ERS, GOLD and ATS criteria in relation to doctor's diagnosis, symptoms, age, gender, and smoking habits. *Respiration* 2005; 72: 471-479.
27. Yin P, Jiang CQ, Cheng KK, Lam TH, Lam KH, Miller MR, Zhang WS, Thomas GN, Adab P. Passive smoking exposure and risk of COPD among adults in China: the Guangzhou Biobank Cohort Study. *Lancet* 2007; 370: 751-757.
28. Hu G, Zhou Y, Tian J, Yao W, Li J, Li B, Ran P. Risk of COPD from exposure to biomass smoke: a metaanalysis. *Chest* 2010; 138: 20-31.
29. Frazer K, Callinan JE, McHugh J, van Baarsel S, Clarke A, Doherty K, Kelleher C. Legislative smoking bans for reducing harms from secondhand smoke exposure, smoking prevalence and tobacco consumption. *Cochrane Database Syst Rev* 2016; 2: CD005992.
30. Camp PG, Ramirez-Venegas A, Sansores RH, Alva LF, McDougall JE, Sin DD, Paré PD, Müller NL, Silva CI, Rojas CE, Coxson HO. COPD phenotypes in biomass smoke- versus tobacco smoke-exposed Mexican women. *Eur Respir J* 2014; 43: 725-734.
31. Fernandes L, Gulati N, Fernandes Y, Mesquita AM, Sardessai M, Lammers JJ, Mohamed Hoesein FA, Ten Hacken NHT, van den Berge M, Galbán CJ, Siddiqui S. Small airway imaging phenotypes in biomass- and tobacco smoke-exposed patients with COPD. *ERJ Open Res* 2017; 3.
32. Morgan WJ, Stern DA, Sherrill DL, Guerra S, Holberg CJ, Guilbert TW, Taussig LM, Wright AL, Martinez FD. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med* 2005; 172: 1253-1258.
33. Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, Cowan JO, Herbison GP, Silva PA, Poulton R. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003; 349: 1414-1422.
34. Tai A, Tran H, Roberts M, Clarke N, Wilson J, Robertson CF. The association between childhood asthma and adult chronic obstructive pulmonary disease. *Thorax* 2014; 69: 805-810.
35. Bisgaard H, Jensen SM, Bønnelykke K. Interaction between asthma and lung function growth in early life. *Am J Respir Crit Care Med* 2012; 185: 1183-1189.
36. Svanes C, Sunyer J, Plana E, Dharmage S, Heinrich J, Jarvis D, de Marco R, Norbäck D, Raherison C, Villani S, Wjst M, Svanes K, Antó JM. Early life origins of chronic obstructive pulmonary disease. *Thorax* 2010; 65: 14-20.
37. McGeachie MJ, Yates KP, Zhou X, Guo F, Sternberg AL, Van Natta ML, Wise RA, Szefler SJ, Sharma S, Kho AT, Cho MH, Croteau-Chonka DC, Castaldi PJ, Jain G, Sanyal A, Zhan Y, Lajoie BR, Dekker J, Stamatoyannopoulos J, Covar RA, Zeiger RS, Adkinson NF, Williams PV, Kelly HW, Grasemann H, Vonk JM, Koppelman GH, Postma DS, Raby BA, Houston I, Lu Q, Fuhlbrigge AL, Tantisira KG, Silverman EK, Tonascia J, Weiss ST, Strunk RC. Patterns of Growth and Decline in Lung Function in Persistent Childhood Asthma. *N Engl J Med* 2016; 374: 1842-1852.

38. Bui DS, Lodge CJ, Burgess JA, Lowe AJ, Perret J, Bui MQ, Bowatte G, Gurrin L, Johns DP, Thompson BR, Hamilton GS, Frith PA, James AL, Thomas PS, Jarvis D, Svanes C, Russell M, Morrison SC, Feather I, Allen KJ, Wood-Baker R, Hopper J, Giles GG, Abramson MJ, Walters EH, Matheson MC, Dharmage SC. Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. *Lancet Respir Med* 2018.
39. Ross JC, Castaldi PJ, Cho MH, Hersh CP, Rahaghi FN, Sanchez-Ferrero GV, Parker MM, Litonjua AA, Sparrow D, Dy JG, Silverman EK, Washko GR, San Jose Estepar R. Longitudinal Modeling of Lung Function Trajectories in Smokers with and without COPD. *Am J Respir Crit Care Med* 2018.
40. Jenkins CR, Chapman KR, Donohue JF, Roche N, Tsiligianni I, Han MK. Improving the Management of COPD in Women. *Chest* 2017; 151: 686-696.
41. Kohansal R, Martinez-Camblor P, Agusti A, Buist AS, Mannino DM, Soriano JB. The natural history of chronic airflow obstruction revisited: an analysis of the Framingham offspring cohort. *Am J Respir Crit Care Med* 2009; 180: 3-10.
42. Vollmer WM, Enright PL, Pedula KL, Speizer F, Kuller LH, Kiley J, Weinmann GG. Race and gender differences in the effects of smoking on lung function. *Chest* 2000; 117: 764-772.
43. Gan WQ, Man SF, Postma DS, Camp P, Sin DD. Female smokers beyond the perimenopausal period are at increased risk of chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Respir Res* 2006; 7: 52.
44. Sørheim IC, Johannessen A, Gulsvik A, Bakke PS, Silverman EK, DeMeo DL. Gender differences in COPD: are women more susceptible to smoking effects than men? *Thorax* 2010; 65: 480-485.
45. Amaral AFS, Strachan DP, Burney PGJ, Jarvis DL. Female Smokers Are at Greater Risk of Airflow Obstruction Than Male Smokers. UK Biobank. *Am J Respir Crit Care Med* 2017; 195: 1226-1235.
46. Tan WC, Sin DD, Bourbeau J, Hernandez P, Chapman KR, Cowie R, FitzGerald JM, Marciniuk DD, Maltais F, Buist AS, Road J, Hogg JC, Kirby M, Coxson H, Hague C, Leipsic J, O'Donnell DE, Aaron SD, Group CCR. Characteristics of COPD in never-smokers and ever-smokers in the general population: results from the CanCOLD study. *Thorax* 2015; 70: 822-829.
47. Connett JE, Murray RP, Buist AS, Wise RA, Bailey WC, Lindgren PG, Owens GR, Group LHSR. Changes in smoking status affect women more than men: results of the Lung Health Study. *Am J Epidemiol* 2003; 157: 973-979.
48. Vozoris NT, Stanbrook MB. Smoking prevalence, behaviours, and cessation among individuals with COPD or asthma. *Respir Med* 2011; 105: 477-484.
49. Tsiligianni I, Mezzi K, Fucile S, Kostikas K, Shen S, Banerji D, Fogel R. Response to Indacaterol/Glycopyrronium (IND/GLY) by Sex in Patients with COPD: A Pooled Analysis from the IGNITE Program. *COPD* 2017; 14: 375-381.
50. Jin K. Modern Biological Theories of Aging. *Aging Dis* 2010; 1: 72-74.
51. Bellia V, Pistelli R, Catalano F, Antonelli-Incalzi R, Grassi V, Melillo G, Olivieri D, Rengo F. Quality control of spirometry in the elderly. The SA.R.A. study. SAlute Respiration nell'Anziano = Respiratory Health in the Elderly. *Am J Respir Crit Care Med* 2000; 161: 1094-1100.

52. Board M, Allen SC. A simple drawing test to identify patients who are unlikely to be able to learn to use an inhaler. *Int J Clin Pract* 2006; 60: 510-513.
53. Malmberg LP, Rytilä P, Happonen P, Haahtela T. Inspiratory flows through dry powder inhaler in chronic obstructive pulmonary disease: age and gender rather than severity matters. *Int J Chron Obstruct Pulmon Dis* 2010; 5: 257-262.
54. Gershon A, Croxford R, Calzavara A, To T, Stanbrook MB, Upshur R, Stukel TA. Cardiovascular safety of inhaled long-acting bronchodilators in individuals with chronic obstructive pulmonary disease. *JAMA Intern Med* 2013; 173: 1175-1185.
55. Vestbo J, Anderson W, Coxson HO, Crim C, Dawber F, Edwards L, Hagan G, Knobil K, Lomas DA, MacNee W, Silverman EK, Tal-Singer R, investigators E. Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE). *Eur Respir J* 2008; 31: 869-873.
56. Regan EA, Hokanson JE, Murphy JR, Make B, Lynch DA, Beaty TH, Curran-Everett D, Silverman EK, Crapo JD. Genetic epidemiology of COPD (COPDGene) study design. *COPD* 2010; 7: 32-43.
57. Couper D, LaVange LM, Han M, Barr RG, Bleecker E, Hoffman EA, Kanner R, Kleerup E, Martinez FJ, Woodruff PG, Rennard S, Group SR. Design of the Subpopulations and Intermediate Outcomes in COPD Study (SPIROMICS). *Thorax* 2014; 69: 491-494.
58. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, Pinto Plata V, Cabral HJ. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004; 350: 1005-1012.
59. Bourbeau J, Tan WC, Benedetti A, Aaron SD, Chapman KR, Coxson HO, Cowie R, Fitzgerald M, Goldstein R, Hernandez P, Leipsic J, Maltais F, Marciniuk D, O'Donnell D, Sin DD, Cancold Study G. Canadian Cohort Obstructive Lung Disease (CanCOLD): Fulfilling the need for longitudinal observational studies in COPD. *COPD* 2014; 11: 125-132.
60. Martinez FJ, Fabbri LM, Ferguson GT, Orevillo C, Darken P, Martin UJ, Reisner C. Baseline Symptom Score Impact on Benefits of Glycopyrrolate/Formoterol Metered Dose Inhaler in COPD. *Chest* 2017; 152: 1169-1178.
61. Valipour A, Slebos DJ, Herth F, Darwiche K, Wagner M, Ficker JH, Petermann C, Hubner RH, Stanzel F, Eberhardt R, Team IS. Endobronchial Valve Therapy in Patients with Homogeneous Emphysema. Results from the IMPACT Study. *Am J Respir Crit Care Med* 2016; 194: 1073-1082.
62. Kemp SV, Slebos DJ, Kirk A, Kornaszewska M, Carron K, Ek L, Broman G, Hillerdal G, Mal H, Pison C, Briault A, Downer N, Darwiche K, Rao J, Hubner RH, Ruwwe-Glosenkamp C, Trosini-Desert V, Eberhardt R, Herth FJ, Derom E, Malfait T, Shah PL, Garner JL, Ten Hacken NH, Fallouh H, Leroy S, Marquette CH, * TST. A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (TRANSFORM). *Am J Respir Crit Care Med* 2017; 196: 1535-1543.
63. Pavord ID, Chanez P, Criner GJ, Kerstjens HAM, Korn S, Lugogo N, Martinot JB, Sagara H, Albers FC, Bradford ES, Harris SS, Mayer B, Rubin DB, Yancey SW, Sciurba FC. Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2017; 377: 1613-1629.
64. Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol

in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. *Lancet Respir Med* 2015; 3: 435-442.
65. Bafadhel M, McKenna S, Terry S, Mistry V, Pancholi M, Venge P, Lomas DA, Barer MR, Johnston SL, Pavord ID, Brightling CE. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. *Am J Respir Crit Care Med* 2012; 186: 48-55.
66. Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, Dransfield MT, Halpin DMG, Han MK, Jones CE, Kilbride S, Lange P, Lomas DA, Martinez FJ, Singh D, Tabberer M, Wise RA, Pascoe SJ, Investigators I. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. *N Engl J Med* 2018.
67. Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, Humbert M, Jones P, Gibson PG, Vestbo J, Beasley R, Pavord ID. Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J* 2016; 47: 410-419.
68. Calzetta L, Ora J, Cavalli F, Rogliani P, O'Donnell DE, Cazzola M. Impact of LABA/LAMA combination on exercise endurance and lung hyperinflation in COPD: A pair-wise and network meta-analysis. *Respir Med* 2017; 129: 189-198.
69. Calzetta L, Rogliani P, Matera MG, Cazzola M. A Systematic Review With Meta-Analysis of Dual Bronchodilation With LAMA/LABA for the Treatment of Stable COPD. *Chest* 2016; 149: 1181-1196.
70. van Noord JA, Aumann JL, Janssens E, Verhaert J, Smeets JJ, Mueller A, Cornelissen PJ. Effects of tiotropium with and without formoterol on airflow obstruction and resting hyperinflation in patients with COPD. *Chest* 2006; 129: 509-517.
71. Agusti A, Hedner J, Marin JM, Barbé F, Cazzola M, Rennard S. Night-time symptoms: a forgotten dimension of COPD. *Eur Respir Rev* 2011; 20: 183-194.
72. Reisner C, Gottschlich G, Fakih F, Koser A, Krainson J, Delacruz L, Arora S, Feldman G, Pudi K, Siddiqui S, Orevillo C, Maes A, St Rose E, Martin U. 24-h bronchodilation and inspiratory capacity improvements with glycopyrrolate/formoterol fumarate via co-suspension delivery technology in COPD. *Respir Res* 2017; 18: 157.
73. Zhou Y, Zhong NS, Li X, Chen S, Zheng J, Zhao D, Yao W, Zhi R, Wei L, He B, Zhang X, Yang C, Li Y, Li F, Du J, Gui J, Hu B, Bai C, Huang P, Chen G, Xu Y, Wang C, Liang B, Hu G, Tan H, Ye X, Ma X, Chen Y, Hu X, Tian J, Zhu X, Shi Z, Du X, Li M, Liu S, Yu R, Zhao J, Ma Q, Xie C, Chen T, Lin Y, Zeng L, Ye C, Ye W, Luo X, Yu S, Guan WJ, Ran P. Tiotropium in Early-Stage Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2017; 377: 923-935.
74. Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A, Anderson J, Maden C, group ToISAl-abas. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003; 361: 449-456.
75. Jones PW, Willits LR, Burge PS, Calverley PM, investigators ISiOLDiEs. Disease severity and the effect of fluticasone propionate on chronic obstructive pulmonary disease exacerbations. *Eur Respir J* 2003; 21: 68-73.
76. Lipson DA, Barnacle H, Birk R, Brealey N, Locantore N, Lomas DA, Ludwig-Sengpiel A, Mohindra R, Tabberer M, Zhu CQ, Pascoe SJ. FULFIL Trial: Once-Daily Triple Therapy for Patients with Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2017; 196: 438-446.

77. Singh D, Papi A, Corradi M, Pavlišová I, Montagna I, Francisco C, Cohuet G, Vezzoli S, Scuri M, Vestbo J. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. *Lancet* 2016; 388: 963-973.
78. Papi A, Vestbo J, Fabbri L, Corradi M, Prunier H, Cohuet G, Guasconi A, Montagna I, Vezzoli S, Petruzzelli S, Scuri M, Roche N, Singh D. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. *Lancet* 2018; 391: 1076-1084.
79. Dransfield MT, Bourbeau J, Jones PW, Hanania NA, Mahler DA, Vestbo J, Wachtel A, Martinez FJ, Barnhart F, Sanford L, Lettis S, Crim C, Calverley PM. Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. *Lancet Respir Med* 2013; 1: 210-223.
80. Price D, Yawn B, Brusselle G, Rossi A. Risk-to-benefit ratio of inhaled corticosteroids in patients with COPD. *Prim Care Respir J* 2013; 22: 92-100.
81. Yang IA, Clarke MS, Sim EH, Fong KM. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012; 7: CD002991.
82. Brode SK, Campitelli MA, Kwong JC, Lu H, Marchand-Austin A, Gershon AS, Jamieson FB, Marras TK. The risk of mycobacterial infections associated with inhaled corticosteroid use. *Eur Respir J* 2017; 50.
83. Rossi A, van der Molen T, del Olmo R, Papi A, Wehbe L, Quinn M, Lu C, Young D, Cameron R, Bucchioni E, Altman P. INSTEAD: a randomised switch trial of indacaterol versus salmeterol/fluticasone in moderate COPD. *Eur Respir J* 2014; 44: 1548-1556.
84. Nadeem NJ, Taylor SJ, Eldridge SM. Withdrawal of inhaled corticosteroids in individuals with COPD--a systematic review and comment on trial methodology. *Respir Res* 2011; 12: 107.
85. Magnussen H, Disse B, Rodriguez-Roisin R, Kirsten A, Watz H, Tetzlaff K, Towse L, Finnigan H, Dahl R, Decramer M, Chanez P, Wouters EF, Calverley PM, Investigators W. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. *N Engl J Med* 2014; 371: 1285-1294.
86. Calverley PMA, Tetzlaff K, Vogelmeier C, Fabbri LM, Magnussen H, Wouters EFM, Mezzanotte W, Disse B, Finnigan H, Asijee G, Hallmann C, Watz H. Eosinophilia, Frequent Exacerbations, and Steroid Response in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2017; 196: 1219-1221.
87. Vestbo J, Papi A, Corradi M, Blazhko V, Montagna I, Francisco C, Cohuet G, Vezzoli S, Scuri M, Singh D. Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial. *Lancet* 2017; 389: 1919-1929.
88. Lacoste JY, Bousquet J, Chanez P, Van Vyve T, Simony-Lafontaine J, Lequeu N, Vic P, Enander I, Godard P, Michel FB. Eosinophilic and neutrophilic inflammation in asthma, chronic bronchitis, and chronic obstructive pulmonary disease. *J Allergy Clin Immunol* 1993; 92: 537-548.

89. Saetta M, Di Stefano A, Maestrelli P, Turato G, Ruggieri MP, Roggeri A, Calcagni P, Mapp CE, Ciaccia A, Fabbri LM. Airway eosinophilia in chronic bronchitis during exacerbations. *Am J Respir Crit Care Med* 1994; 150: 1646-1652.
90. Vedel-Krogh S, Nielsen SF, Lange P, Vestbo J, Nordestgaard BG. Blood Eosinophils and Exacerbations in Chronic Obstructive Pulmonary Disease. The Copenhagen General Population Study. *Am J Respir Crit Care Med* 2016; 193: 965-974.
91. Zysman M, Deslee G, Caillaud D, Chanez P, Escamilla R, Court-Fortune I, Nesme-Meyer P, Perez T, Paillasseur JL, Pinet C, Jebrak G, Roche N, Burgel PR. Relationship between blood eosinophils, clinical characteristics, and mortality in patients with COPD. *Int J Chron Obstruct Pulmon Dis* 2017; 12: 1819-1824.
92. Casanova C, Celli BR, de-Torres JP, Martínez-Gonzalez C, Cosio BG, Pinto-Plata V, de Lucas-Ramos P, Divo M, Fuster A, Peces-Barba G, Calle-Rubio M, Solanes I, Aguero R, Feu-Collado N, Alfageme I, De Diego A, Romero A, Balcells E, Llunell A, Galdiz JB, Marin M, Moreno A, Cabrera C, Golpe R, Lacarcel C, Soriano JB, López-Campos JL, Soler-Cataluña JJ, Marin JM. Prevalence of persistent blood eosinophilia: relation to outcomes in patients with COPD. *Eur Respir J* 2017; 50.
93. Barnes NC, Sharma R, Lettis S, Calverley PM. Blood eosinophils as a marker of response to inhaled corticosteroids in COPD. *Eur Respir J* 2016; 47: 1374-1382.
94. Suzuki M, Makita H, Konno S, Shimizu K, Kimura H, Nishimura M, Investigators HCCS. Asthma-like Features and Clinical Course of Chronic Obstructive Pulmonary Disease. An Analysis from the Hokkaido COPD Cohort Study. *Am J Respir Crit Care Med* 2016; 194: 1358-1365.
95. Shaaban H, Daniel S, Sison R, Slim J, Perez G. Eosinopenia: Is it a good marker of sepsis in comparison to procalcitonin and C-reactive protein levels for patients admitted to a critical care unit in an urban hospital? *J Crit Care* 2010; 25: 570-575.
96. Steer J, Gibson J, Bourke SC. The DECAF Score: predicting hospital mortality in exacerbations of chronic obstructive pulmonary disease. *Thorax* 2012; 67: 970-976.
97. Holland M, Alkhalil M, Chandromouli S, Janjua A, Babores M. Eosinopenia as a marker of mortality and length of stay in patients admitted with exacerbations of chronic obstructive pulmonary disease. *Respirology* 2010; 15: 165-167.
98. Siddiqui SH, Guasconi A, Vestbo J, Jones P, Agusti A, Paggiaro P, Wedzicha JA, Singh D. Blood Eosinophils: A Biomarker of Response to Extrafine Beclomethasone/Formoterol in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2015; 192: 523-525.
99. Bafadhel M, Peterson S, De Blas MA, Calverley PM, Rennard SI, Richter K, Fageras M. Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. *Lancet Respir Med* 2018; 6: 117-126.
100. Roche N, Chapman KR, Vogelmeier CF, Herth FJF, Thach C, Fogel R, Olsson P, Patalano F, Banerji D, Wedzicha JA. Blood Eosinophils and Response to Maintenance Chronic Obstructive Pulmonary Disease Treatment. Data from the FLAME Trial. *Am J Respir Crit Care Med* 2017; 195: 1189-1197.
101. Watz H, Tetzlaff K, Wouters EF, Kirsten A, Magnussen H, Rodriguez-Roisin R, Vogelmeier C, Fabbri LM, Chanez P, Dahl R, Disse B, Finnigan H, Calverley PM. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of

inhaled corticosteroids: a post-hoc analysis of the WISDOM trial. *Lancet Respir Med* 2016; 4: 390-398.
102. Singh D, Kolsum U, Brightling CE, Locantore N, Agusti A, Tal-Singer R, investigators E. Eosinophilic inflammation in COPD: prevalence and clinical characteristics. *Eur Respir J* 2014; 44: 1697-1700.
103. Southworth T, Beech G, Foden P, Kolsum U, Singh D. The reproducibility of COPD blood eosinophil counts. *Eur Respir J* 2018.
104. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987; 106: 196-204.
105. Paggiaro PL, Dahle R, Bakran I, Frith L, Hollingworth K, Efthimiou J. Multicentre randomised placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease. International COPD Study Group. *Lancet* 1998; 351: 773-780.
106. Rodriguez-Roisin R. Toward a consensus definition for COPD exacerbations. *Chest* 2000; 117: 398S-401S.
107. Burge S, Wedzicha JA. COPD exacerbations: definitions and classifications. *Eur Respir J Suppl* 2003; 41: 46s-53s.
108. Beghé B, Verduri A, Roca M, Fabbri LM. Exacerbation of respiratory symptoms in COPD patients may not be exacerbations of COPD. *Eur Respir J* 2013; 41: 993-995.
109. Noell G, Cosio BG, Faner R, Monso E, Peces-Barba G, de Diego A, Esteban C, Gea J, Rodriguez-Roisin R, Garcia-Nunez M, Pozo-Rodriguez F, Kalko SG, Agusti A. Multi-level differential network analysis of COPD exacerbations. *Eur Respir J* 2017; 50.
110. Celli B. Dissecting COPD exacerbations: Time to rethink our definition. *Eur Resp J* 2017; 50: Sept.
111. Ball P. Epidemiology and treatment of chronic bronchitis and its exacerbations. *Chest* 1995; 108: 43S-52S.
112. Wilkinson TM, Hurst JR, Perera WR, Wilks M, Donaldson GC, Wedzicha JA. Effect of interactions between lower airway bacterial and rhinoviral infection in exacerbations of COPD. *Chest* 2006; 129: 317-324.
113. Ram FS, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC. Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006: CD004403.
114. Walters JA, Gibson PG, Wood-Baker R, Hannay M, Walters EH. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2009: CD001288.
115. Mathioudakis AG, Amanetopoulou SG, Gialmanidis IP, Chatzimavridou-Grigoriadou V, Siasos G, Evangelopoulou E, Mathioudakis GA. Impact of long-term treatment with low-dose inhaled corticosteroids on the bone mineral density of chronic obstructive pulmonary disease patients: aggravating or beneficial? *Respirology* 2013; 18: 147-153.
116. Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JA, Criner GJ, Curtis JL, Dransfield MT, Han MK, Lazarus SC, Make B, Marchetti N, Martinez FJ, Madinger NE, McEvoy C, Niewoehner DE, Porsasz J, Price CS, Reilly J, Scanlon PD, Sciurba FC, Scharf SM, Washko

GR, Woodruff PG, Anthonisen NR, Network CCR. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med* 2011; 365: 689-698.
117. Fabbri LM, Calverley PM, Izquierdo-Alonso JL, Bundschuh DS, Brose M, Martinez FJ, Rabe KF, groups M-aM-s. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials. *Lancet* 2009; 374: 695-703.
118. Martinez FJ, Rabe KF, Sethi S, Pizzichini E, McIvor A, Anzueto A, Alagappan VK, Siddiqui S, Rekeda L, Miller CJ, Zetterstrand S, Reisner C, Rennard SI. Effect of Roflumilast and Inhaled Corticosteroid/Long-Acting β2-Agonist on Chronic Obstructive Pulmonary Disease Exacerbations (RE(2)SPOND). A Randomized Clinical Trial. *Am J Respir Crit Care Med* 2016; 194: 559-567.
119. Tse HN, Raiteri L, Wong KY, Yee KS, Ng LY, Wai KY, Loo CK, Chan MH. High-dose N-acetylcysteine in stable COPD: the 1-year, double-blind, randomized, placebo-controlled HIACE study. *Chest* 2013; 144: 106-118.
120. Zheng JP, Wen FQ, Bai CX, Wan HY, Kang J, Chen P, Yao WZ, Ma LJ, Li X, Raiteri L, Sardina M, Gao Y, Wang BS, Zhong NS, group Ps. Twice daily N-acetylcysteine 600 mg for exacerbations of chronic obstructive pulmonary disease (PANTHEON): a randomised, double-blind placebo-controlled trial. *Lancet Respir Med* 2014; 2: 187-194.
121. Zheng JP, Kang J, Huang SG, Chen P, Yao WZ, Yang L, Bai CX, Wang CZ, Wang C, Chen BY, Shi Y, Liu CT, Chen P, Li Q, Wang ZS, Huang YJ, Luo ZY, Chen FP, Yuan JZ, Yuan BT, Qian HP, Zhi RC, Zhong NS. Effect of carbocisteine on acute exacerbation of chronic obstructive pulmonary disease (PEACE Study): a randomised placebo-controlled study. *Lancet* 2008; 371: 2013-2018.
122. Zhou YM, Wang XP, Zeng XY, Qiu R, Xie JF, Liu SM, Zheng JP, Zhong NS, Ran PX. [Theophylline in the treatment of chronic obstructive pulmonary disease: a randomized, double-blind, placebo-controlled study]. *Zhonghua Jie He He Hu Xi Za Zhi* 2006; 29: 577-582.
123. Cosio BG, Shafiek H, Iglesias A, Yanez A, Cordova R, Palou A, Rodriguez-Roisin R, Peces-Barba G, Pascual S, Gea J, Sibila O, Barnes PJ, Agusti A. Oral Low-dose Theophylline on Top of Inhaled Fluticasone-Salmeterol Does Not Reduce Exacerbations in Patients With Severe COPD: A Pilot Clinical Trial. *Chest* 2016; 150: 123-130.
124. Turner MO, Patel A, Ginsburg S, FitzGerald JM. Bronchodilator delivery in acute airflow obstruction. A meta-analysis. *Arch Intern Med* 1997; 157: 1736-1744.
125. Niewoehner DE, Erbland ML, Deupree RH, Collins D, Gross NJ, Light RW, Anderson P, Morgan NA. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. *N Engl J Med* 1999; 340: 1941-1947.
126. Alia I, de la Cal MA, Esteban A, Abella A, Ferrer R, Molina FJ, Torres A, Gordo F, Elizalde JJ, de Pablo R, Huete A, Anzueto A. Efficacy of corticosteroid therapy in patients with an acute exacerbation of chronic obstructive pulmonary disease receiving ventilatory support. *Arch Intern Med* 2011; 171: 1939-1946.
127. Thompson WH, Nielson CP, Carvalho P, Charan NB, Crowley JJ. Controlled trial of oral prednisone in outpatients with acute COPD exacerbation. *Am J Respir Crit Care Med* 1996; 154: 407-412.

128. Leuppi JD, Schuetz P, Bingisser R, Bodmer M, Briel M, Drescher T, Duerring U, Henzen C, Leibbrandt Y, Maier S, Miedinger D, Muller B, Scherr A, Schindler C, Stoeckli R, Viatte S, von Garnier C, Tamm M, Rutishauser J. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. *JAMA* 2013; 309: 2223-2231.
129. de Jong YP, Uil SM, Grotjohan HP, Postma DS, Kerstjens HA, van den Berg JW. Oral or IV prednisolone in the treatment of COPD exacerbations: a randomized, controlled, double-blind study. *Chest* 2007; 132: 1741-1747.
130. Vollenweider DJ, Jarrett H, Steurer-Stey CA, Garcia-Aymerich J, Puhan MA. Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012; 12: CD010257.
131. Malerba M, Nardin M, Radaeli A, Montuschi P, Carpagnano GE, Clini E. The potential role of endothelial dysfunction and platelet activation in the development of thrombotic risk in COPD patients. *Expert review of hematology* 2017: 1-12.
132. Polverino F, Laucho-Contreras ME, Petersen H, Bijol V, Sholl LM, Choi ME, Divo M, Pinto-Plata V, Chetta A, Tesfaigzi Y, Celli BR, Owen CA. A Pilot Study Linking Endothelial Injury in Lungs and Kidneys in Chronic Obstructive Pulmonary Disease. *American journal of respiratory and critical care medicine* 2017; 195: 1464-1476.
133. Zoccali C, Vanholder R, Massy ZA, Ortiz A, Sarafidis P, Dekker FW, Fliser D, Fouque D, Heine GH, Jager KJ, Kanbay M, Mallamaci F, Parati G, Rossignol P, Wiecek A, London G. The systemic nature of CKD. *Nature reviews Nephrology* 2017; 13: 344-358.
134. Divo M, Cote C, de Torres JP, Casanova C, Marin JM, Pinto-Plata V, Zulueta J, Cabrera C, Zagaceta J, Hunninghake G, Celli B, Group BC. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012; 186: 155-161.