2nd INTERNATIONAL WORKSHOP ON LUNG HEALTH
COPD: NEW CHALLENGES, NEW SOLUTIONS

VALENCIA, 19-21 FEBRUARY, 2015

ABSTRACT BOOK

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EFFECTIVENESS OF A SELF-TREATMENT PROGRAMME FOR THE REDUCTION OF SEVERE EXACERBATIONS IN PATIENTS WITH COPD

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Introduction and objectives: The treatment of COPD requires multiple interventions. Non-pharmacological interventions can improve health indicators and save care resources.

Material and methods: A multicentre, randomized, single-blind, parallel-group clinical trial with a one-year follow-up of a self-treatment programme (STP) versus conventional management. The STP intervention group included a group education centre, three specific consultations, training in inhaler technique and a written treatment plan. The control group received standard care. The main variable was the severe exacerbations rate. Secondary variables were the exacerbations rate, number of admissions and mortality.

Results: Of the 250 patients recruited, 101 (40.4%) were included in the trial; 38 (37.62%) patients in the control group completed the trial and 47 (46.53%) in the intervention group. There were no significant differences in the baseline characteristics of the patients: age, BMI, smoking, FEV_1, dyspnoea (MRC), quality of life (CAT) and GOLD classification. Twenty (52.6%) patients in the control group presented severe exacerbations vs 19 (40.4%) in the intervention group (*P*=0.262). Thirty-one patients (81.6%) in the control group presented moderate or severe exacerbations vs 33 (70.2%) in the intervention group (*P*=0.227). Sixteen patients (42.1%) in the control group were hospitalised vs 12 (25.5%) in the intervention group (*P*=0.106). Two patients (5.26%) in the control group died vs none in the intervention group (*P*=0.383). The severe exacerbations rate was 1.37 (1.02–1.79) in the control group vs 0.89 (0.64-1.21) in the intervention group (*P*=0.049) (rate ratio, 1.53 [1.01-2.29]). The exacerbations rate in the control group was 4.29 (3.5-5.11) vs 2.59 (2.12-3.15) in the intervention group (*P*=0.002) (rate ratio, 1.56 [1.27-2.14]). The NNT (STP vs conventional treatment) to prevent one severe exacerbation per year was 6.25 (5.0-8.0).

Conclusions:

1. In the first year, the STP reduced the severe exacerbations rate in patients with COPD.
2. The STP reduced the number of hospitalisations and of moderate and severe exacerbations.
3. The STP could be used in less than half of the selected population.

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PREVALENCE OF CHRONIC BRONCHITIS IN SWEDEN: SMOKING AND SOCIAL CLASS MAJOR DETERMINANTS BUT NO GENDER DIFFERENCE ANY MORE

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Background: Chronic bronchitis is a common disease associated with impaired quality of life, hospitalizations and increased mortality. However, it has been less in focus after the introduction of the term chronic obstructive pulmonary disease (COPD). Today the taxonomy is under discussion and some researchers now regard chronic bronchitis as a symptom combination, while others still recognize it as a disease entity. There are no recent published data on the prevalence of chronic bronchitis from the Scandinavian countries.

Aim: Study the prevalence of chronic bronchitis and associated determinants in the general adult population in West Sweden.

Methods: From the 18 087 questionnaire responders out of 30 000 invited to participate at the West Sweden Asthma Study (WSAS), 2000 subjects were randomly selected and invited to detailed clinical examinations performed 2009-2013. 1172 subjects aged 17-79 years participated at the examinations which included, among others, spirometry and structured interviews. A separate study found no major bias caused by non-response. Chronic bronchitis was defined according to the WHO definition, which is similar to the CIBA Guest Symposium agreement from 1959.

Results: The prevalence of chronic bronchitis was 7.2% (men 7.6%; women 6.8%, ns), and it was 8.7% in age >60 years. Chronic bronchitis was strongly associated with smoking defined both as current smoking status and pack-years. Other risk factors were increasing age, low socio-economic class, urban living and occupational exposure to gas, dust or fumes. Of those with chronic bronchitis, 22% fulfilled the GOLD criteria of COPD.

Conclusion: The prevalence of chronic bronchitis was somewhat lower than found by studies in Sweden in the 1980s. Interestingly, in contrast to previous studies the prevalence was now similar in men and women. Although smoking still being the dominating risk factor for chronic bronchitis, the relative importance of smoking had decreased parallel with a decreasing smoking prevalence, while the relative importance of other factors than smoking had increased compared to previous studies.

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ADHERENCE AND PERCEPTION OF PHYSIOTHERAPY IN CYSTIC FIBROSIS PATIENTS

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Background/Aims: Cystic fibrosis (CF) is a chronic and multisystem disease that affects the mucociliary clearance. Respiratory physiotherapy (RP) has revealed as one of the main pillars of treatment. This study was aimed at assessing the convergent validity and the internal consistency of a new instrument (CAP-FISIO questionnaire) to measure the adherence and the perception of RP technics from the point of view of CF patients. In addition, we inquired into the correlation of the CAP-FISIO questionnaire outcomes with degrees of self-efficacy and coping of the patients.

Methods: This is a descriptive cross-sectional pilot study approved by Ethic Committee ascribed to the Universidad Autónoma de Madrid. CF patients were assessed in one temporal moment: 1) anthropometrics; 2) forced spirometry; 3) adherence and perception of RP treatment by CAP-FISIO questionnaire; 4) self-efficacy scale for stress coping (EAEAE); 5) coping strategies questionnaire (COPE-28), in order to analyse validity and internal consistency of the questionnaire by means of other validated questionnaires.

Results: The analysed sample consisted of 44 CF patients (mean ± standard deviation): age (25.8±10.9 years); BMI (17.8±7.6 Kg/m^2); FVC (3.2±0.8 L and 83.8±17.3 %); FEV_1 (2.1±0.7 L and 65.5±23.2 %); FEV_1/FVC (67.4±14.0 %). The overall internal consistency of the CAP-FISIO questionnaire was quite good (α=0.896), as well as for the constructs $CAP\text{-}FISIO_{adherence}$ (α=0.870) and $CAP\text{-}FISIO_{perception}$ (α=0.826). Significant correlations were found between the following parameters: Age [$CAP\text{-}FISIO_{total}$ (ρ=0.555; p=0.000), $CAP\text{-}FISIO_{perception}$ (ρ=0.479; p=0.002), $CAP\text{-}FISIO_{adherence}$ (ρ=0.529; p=0.001) and $COPE\text{-}28_{total}$ (ρ=0.532; p=0.001)]; $CAP\text{-}FISIO_{total}$ [$COPE\text{-}28_{total}$ (ρ=0.310; p=0.041)] and $CAP\text{-}FISIO_{adherence}$ [$COPE\text{-}28_{total}$ (ρ=0.306; p=0.043)].

Conclusions: Our results point out that the new questionnaire CAP-FISIO has a good internal consistency to measure the adherence and perception degree to RP techniques. Older patients showed a high correlation with adherence and perception degree to RP techniques and with high coping degrees. In turn, we found a good correlation between the adherence and active coping degrees. Nevertheless these results should be interpreted with caution since this is a preliminary study.

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PATIENTS WITH COPD TRAPPED IN AN INVISIBLE CAGE: A QUALITATIVE STUDY

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Background/Aims: COPD is a major health problem and health burden in the world due to smoking, air pollution and an aging society. COPD will be the third leading cause of death in the world in 2030 (WHO, 2008). The issue of COPD being a health burden should not be neglected. However, very limited studies exist regarding of the lived experiences from patients with COPD. The purpose of this study was to explore this issue.

Methods: A qualitative approach was designed. In-depth interviews were used to collect the data. Ethical approval was obtained from the Human Research Ethics Committee at National Taiwan University Hospital. This study was conducted in a medical center in Taiwan. The participants were a purposive sample of fourteen patients who were selected from the wards of thoracic, general medicine and geriatrics from January 2013 to January 2014. Semi-structured, face to face, tape-recorded interviews were conducted that ranged from 42 to 120 minutes. Interviews were transcribed verbatim for content analysis to extract the meaning of patients' lived experiences.

Results: Twelve men and two women with COPD were invited to partake in this study. The age range of the participants was 63–86 years old (mean =77.1). According to the GOLD (2014) severity classification of COPD, eight participants were in the mild stage, two were in the moderate stage and five were in the severe stage. The core theme describing the lived experience from patients with COPD was “trapped in an invisible cage”. Five sub-themes were identified: “sense of confinement”, “derailed life”, “time bomb in the winter”, “imminence of the Death” and "striving for wellness" .

Conclusions: This study seeks to provide a better understanding of patients who fight against COPD in an invisible cage. It is anticipated that the finding of this study will help health providers further understand the feeling of patients with COPD. This can also serve as a reference for their care.

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ONCE-DAILY QVA149 IMPROVES LUNG FUNCTION AND DYSPNOEA COMPARED WITH TIOTROPIUM PLUS FORMOTEROL: THE QUANTIFY STUDY

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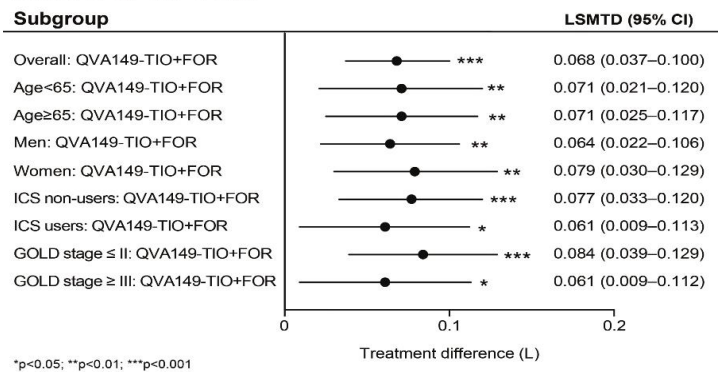
Background: The QUANTIFY study compared QVA149, an approved once-daily (OD) indacaterol [long-acting ß$_2$ agonist (LABA)] plus glycopyrronium [long acting muscarinic antagonist (LAMA)] dual bronchodilator combination, with the free-dose combination of tiotropium plus formoterol (TIO+FOR) regarding lung function, dyspnoea and health-related quality of life in patients with COPD.

Methods: This double-blind, triple-dummy 26-week study randomised patients with moderate-to-severe COPD to QVA149 110/50µg OD or TIO 18µg OD plus FOR 12µg b.i.d. (1:1). Endpoints included pre-dose forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC), transition dyspnoea index (TDI) responder rates and St George's Respiratory Questionnaire-COPD (SGRQ-C).

Results: Of the 934 patients randomised (QVA149 [N=476] and TIO+FOR [N=458]) 87.9% completed the study. Non-inferiority of QVA149 was met with respect to SGRQ-C (least square mean treatment difference [LSMTD] -0.69 units, 95% CI -2.31 to 0.92). QVA149 showed statistically significant improvements in lung function (pre-dose FEV_1: LSMTD=68 mL, p<0.001; pre-dose FVC: LSMTD=74 mL, p<0.01) and TDI responder rates (risk ratio=1.17; p<0.05) versus TIO+FOR. Similarly, QVA149 significantly improved pre-dose FEV_1 irrespective of age, gender, inhaled corticosteroid (ICS) use and COPD severity (Figure 1).

Figure 1: Forest Plot of pre-dose FEV_1 by subgroups (QVA149 vs TIO+FOR)



*p<0.05; **p<0.01; ***p<0.001

Conclusion: QVA149 significantly improved lung function as well as dyspnoea and was non-inferior in improving health-related quality of life compared with TIO+FOR free-dose combination.

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EVALUATION OF EFFICACY AND SAFETY ON DIRECT CHANGE TO GLYCOPYRRONIUM OR A FIXED-DOSE COMBINATION OF INDACATEROL AND GLYCOPYRRONIUM (QVA149) FROM STANDARD COPD THERAPY REGIMEN: RATIONAL AND DESIGN OF CRYSTAL STUDY

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Background: COPD is a progressive disease and many patients remain symptomatic even when treated with current short- or long-acting bronchodilation therapies with or without inhaled corticosteroids. Moreover, current COPD therapies are not always used according to current guidelines which may require treatment changes. These changes to new therapy happen in clinical practice without any washout period, which is different to the evaluation in most phase III clinical trials.

Method/Result: We started a 12-week, prospective, multicenter, randomized clinical trial to evaluate the effect of glycopyrronium (50µg o.d.) or a fixed-dose combination (FDC) of indacaterol and glycopyrronium (110/50µg o.d.; QVA149) in 5712 symptomatic moderate COPD patients who directly switched from their current COPD therapy regimen. The study is executed in an ambulatory setting which allows for a more clinical practice oriented assessment. Following a screening period, patients with moderate COPD are randomized to 4 groups to receive over a period of 90 days either glycopyrronium or QVA149 or remain on their baseline therapy as control, based on COPD symptoms and baseline treatment. Primary study endpoints are: superiority of glycopyrronium vs. short-acting bronchodilators (SABA and/or SAMA as monotherapy or in free or FDC) on trough FEV_1; non-inferiority of glycopyrronium vs. long-acting bronchodilators (LABA or LAMA monotherapy) on trough FEV_1; superiority of QVA149 vs. LABA and ICS in free or FDC on trough FEV_1; superiority of QVA149 vs. long- acting bronchodilators (LABA or LAMA monotherapy) on trough FEV_1. As co-primary endpoint, the transition dyspnea index (TDI) is included in the same statistical evaluation. Furthermore, the COPD Assessment Test (CAT), COPD Clinical Questionnaire (CCQ) and the use of rescue medication beside an e-Diary with other patient reported outcomes are also evaluated.

Conclusion: This study would inform physicians what the results are of a direct change to either glycopyrronium or QVA149 therapy from current COPD therapy regimen in symptomatic, infrequently exacerbating patients with moderate COPD.

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A STUDY DESIGN FOR THE COMPARISON BETWEEN ONCE-DAILY GLYCOPYRRONIUM AND TIOTROPIUM ON MORNING SYMPTOMS AND PULMONARY FUNCTION IN SYMPTOMATIC PATIENTS WITH MODERATE-TO-SEVERE COPD: THE SPRING STUDY

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Background: Morning symptoms in Chronic Obstructive Pulmonary Disease (COPD) are a substantial burden and have an impact on daily life and activities of COPD patients.[1,2] Once-daily glycopyrronium has shown to provide rapid onset and sustained 24-hour bronchodilation in previous studies.[3] The purpose of this study is to compare the efficacy profile of glycopyrronium and tiotropium during the first hours after dosing and their impact on pulmonary function, COPD morning symptoms and ability to perform daily activities by the patient.

Method/Result: This multicenter, blinded, two-period cross-over design study randomised 126 patients with moderate-to-severe COPD to once-daily glycopyrronium (44 µg) or once-daily tiotropium (18 µg) for 28 days. Each treatment duration was 28 days with a wash-out period of 14-19 days in between. The study population consisted of male and female patients (≥40 years) with moderate-to-severe levels of airflow limitation according to the GOLD 2013 criteria and COPD Assessment Test score ≥10. Primary objective was to compare glycopyrronium versus tiotropium in terms of area under the curve between 0 to 4 hours ($AUC_{0\text{-}4h}$) for FEV_1 after first dose. A secondary objective included comparison of glycopyrronium versus tiotropium on COPD symptoms using a patient reported outcomes (PRO) - Early Morning Symptom Diary Questionnaire[4]. Other objectives included assessments of various lung function parameters (Inspiratory capacity [IC], IC $AUC_{0\text{-}4h}$, forced vital capacity, peak IC) and London Chest Activity of Daily Living scale.

Conclusion: The results from this study should elucidate the potential of glycopyrronium versus tiotropium in treating morning symptoms and lung function in moderate-to-severe patients with COPD.

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VITAMIN C AND GLUTATHIONE IN ANTIOXIDANT DEFENCE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND ITS COMORBIDITIES

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Background: The oxidant/antioxidant imbalance plays an important role in the pathogenesis of COPD and its comorbidities. The mechanisms of defence against oxidative damage in COPD are still unclear.

Aim of the Study: The main objective of the study was to assess the systemic antioxidants vitamin C and reduced glutathione (GSH) in chronic obstructive pulmonary disease and its comorbidities.

Methods: Plasmatic vitamin C and GSH were determined in healthy volunteers and COPD patients. Malondialdehyde (MDA) was assessed as an index of oxidative stress. The COPD patients were evaluated according to the presence of comorbidities such as pulmonary hypertension (PH) and cardiovascular disease (CVD).

Results: The biomarker of oxidative stress was found to be significantly ($p \leq 0{,}001$) higher in COPD patients when compared with control group. This increase is more evident in the COPD patients with smoking history. Additionally the highest values of MDA were associated to COPD patients with CVD. COPD patients had a significant ($p<0{,}001$) decrease in antioxidant *status* (vitamin C 1,866±0,353 µg/mL; GSH 0,135±0,022 µmol/mL) when compared with healthy subjects (vitamin C 6,245±0,224 µg/mL; GSH 0,275±0,011 µmol/mL). A decrease in vitamin C was observed in COPD patients with CVD in comparison with COPD patients without PH or CVD. This decrease is more evident in patients with smoking history when compared with non-smokers. GSH levels in COPD patients were decreased in comparison to healthy controls. However, a tendency to an increase in plasmatic GSH was observed in COPD patients with CVD and PH. The involvement of GSH becomes particularly evident in ex-smokers COPD patients with CVD and PH comorbidities.

Conclusions: Oxidative stress may be an important mechanism linking COPD and comorbidities. Plasmatic antioxidants vitamin C and GSH seems to be an important adaptative response to the increase in oxidative stress associated smoking habits and to cardiac injury in COPD.

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SAFETY PROFILE OF GLYCOPYRRONIUM IN PATIENTS WITH COPD: AN INNOVATIVE APPROACH TO ANALYSE DATA FROM POST-MARKETING SURVEILLANCE (PMS)

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Background: Glycopyrronium is a once-daily approved long-acting muscarinic antagonist with rapid onset of action, for maintenance treatment of patients with chronic obstructive pulmonary disease. Based on glycopyrronium cumulative worldwide sales since its launch (upto 28 September 2013), patient exposure to glycopyrronium is estimated to be about 70727 patient treatment years. We evaluated the cardiac safety of glycopyrronium from the post-marketing surveillance.

Methods: Spontaneous voluntary reports of cardiac events were evaluated using the Empirica™ Signal System (ESS), a safety data mining application applied to Novartis global safety database (ARGUS) for automated signal detection and calculating disproportionality scores. ESS utilized the multi-item gamma poisson shrinker (MGPS) algorithm to calculate an estimate of the reporting ratio (EBGM- Empirical Bayes Geometric Mean) of cardiac events considered to be potential risks for the drug. The lower 90% confidence interval limit of EBGM (denoted as EB05) was used. EB05 ≥2 was considered "signalled by MGPS" based on the threshold[1]. Limitation of our method includes potential under reporting and selection of ARGUS database as background.

Results: Based on this innovative signal detection method, glycopyrronium did not show an increased risk of selected cardiovascular adverse events and serious adverse events in patients with chronic obstructive pulmonary disease (Table).

Conclusion: Post marketing data suggests that cardiac safety profile of once-daily glycopyrronium (50µg) is consistent with its current label with an acceptable overall safety profile.

Statistical scores for cardiac safety of glycopyrronium during PMS

Safety Topic	**EB05***
Atrial fibrillation	1.629
Cardiac arrhythmia	1.662
Cardiac failure	0.338
Myocardial infarction	0.185
*all values <2	

Reference:

1. Szarfman A, et al. Drug Saf. 2002;25:381-92

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BRONCHIECTASIS AND COPD: PRELIMINARY STATISTICAL REPORT

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Background/Aims: bronchiectasis often occurs in combination with COPD. The aims of the present study are validate the risk score of bronchiectasis in COPD patients and assess the pathophysiological, microbiological and inflammatory differences in COPD patients with or without bronchiectasis to find biological basis of the specific COPD-bronchiectasis phenotype.

Methods: prospective observational study of 149 patients with COPD clustered on the presence or absence of bronchiectasis was performed at the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico in Milan from October 2011 to November 2011. High Resolution Computer Tomography of chest, pulmonary function test, arterial blood gas analysis and sputum culture were performed for each patient. Serum and exhaled breath condensate (EBC) values of IL1α, IL1β, IL2, IL4, IL6, IL8, IL10, VEGF, IFNγ, EGF, TNFα and MCP1 were measured using high sensitivity RANDOX kit with Biochip Array Technology in a subgroup of 77 patients.

Results: 98 patients (66%) had COPD and bronchiectasis. No difference in clinical and microbiological characteristics were found except for a lower PaO2 in this group (72.31 +/- 1.049 *vs.* 77.62 +/-2.086; *p*=0.013). Median (IQR) IL6 EBC/Serum ratio was higher in patients with COPD and bronchiectasis than COPD alone (0.83 [0.10-1.33] vs 0.16 [0.00-0.56], *p*=0.014, respectively); median (IQR) TNFα EBC/serum ratio was lower in COPD and bronchiectasis than COPD alone, 0.94 (0.59; 4.05) vs 2,32 (0.94; 9.41) *p*=0.015. A higher probability of being affected by bronchiectasis was related to FEV1<50% (OR 5.580), positive sputum (OR 2.656), particularly *S. pneumonia* (OR 3), and b-actine positivity (OR 2.105). Only IL8 and IL6 on serum were independently correlated to bronchiectasis score of severity.

Conclusions: the study confirm that severe COPD patients with a positive sputum culture have an high risk of bronchiectasis. A different local to systemic inflammatory response was found in the two groups, this could be a signal of a biological peculiarity in the pathogenesis of COPD-Bronchiectasis.

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CHRONIC RESPIRATORY FAILURE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE UNDER HOME VENTILATION.

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Background: Home non-invasive ventilation (NIV) is being increasingly used in stable chronic obstructive pulmonary disease (COPD) with chronic hypercapnic respiratory failure (CHRF) although its effectiveness remains debatable.

Aim: to describe a follow-up of COPD patients under NIV for CHRF.

Methods: This is a retrospective descriptive study that included for analysis patients receiving NIV between August 2011 and July 2014 at the Non-invasive Respiratory Care Unit of a university hospital.

Results: Within the 334 patients initially screened, 109 had COPD (32.6%) with a mean±SD postbronchodilator FEV_1 of 38.6±14.9% predicted and a mean±SD age of 65.6±9.6 years.

The mean±SD duration of ventilation was 63.4±51.1months. Coexistence of disorders that can contribute to CHRF was also analysed: obstructive sleep apnea- 59 patients (54.1%), obesity- 41 (37.6%), heart failure- 25 (22.9%), bronchiectasis- 24 (22%), post-tuberculosis sequelae- 9 (8.3%), lung neoplasm- 8 (7.3%) and heterogeneous respiratory and non respiratory diseases- 7 (6.4%).

Sixty-two (56.9%) patients started NIV during admission with acute respiratory failure.

There was significant improvement in mean arterial blood gas values between first stable and final evaluations ($PaCO_2$: 52.9±7.7 *vs* 49.5±7.5mmHg) (p<0.05), with 93.3% of patients compliant to NIV (>4h/day).

There was also a significant increase in mean inspiratory positive airway pressures between baseline and final evaluation (19.5±4.4 *vs.* 23.6±5.3 cmH2O) as well as in breathing frequencies (11.1±4.8 *vs* 15.2±1.4 breath/min) (p<0.0001). At final evaluation, patients with severe hypercapnia (n=47; PCO_2≥50mmHg) performing NIV at higher pressures (n=30; IPAP≥25cmH_2O) were more compliant (mean daily use: 10.1±3.4 *vs.* 6.3±3.7h/day).

During the period under analysis 27 patients died and 15 interrupted NIV due to loss of criteria or noncompliance.

Conclusions: This is a real life retrospective study in COPD patients with CHRF which results suggest benefit from home ventilation. For most of these patients, NIV was tolerable, even at high pressures, and was effective with a significant improvement in arterial blood gases. This study also highlights the heterogeneity of COPD comorbidities which may contribute to CHRF.

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QVA149 IMPROVES DYSPNOEA AND LUNG FUNCTION VERSUS TIOTROPIUM IN SYMPTOMATIC PATIENTS USING LABA/ICS PRECEDING STUDY ENROLMENT: THE BLAZE STUDY

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Background: In the BLAZE study, QVA149 showed superior improvements in dyspnoea (assessed by self-administered computerised transition dyspnoea index [SAC-TDI]) and lung function versus placebo and tiotropium.[1] In this post-hoc analysis, we report these outcomes from the subgroup population using LABA/ICS prior to study enrolment, primarily because of inappropriate use of ICS, despite not being recommended for patients with moderate COPD (GOLD B).

Methods: This blinded, three-period crossover study randomised patients with moderate-to-severe COPD (modified Medical Research Council [mMRC] dyspnoea scale ≥2) to once-daily QVA149 110/50 µg, placebo or tiotropium 18 µg.[1] Outcomes reported were SAC-TDI, forced expiratory volume in 1 second [FEV_1], area under the curve for FEV_1 from 0 to 4 hours [$FEV_1AUC_{0\text{-}4\ h}$], and rescue medication use.

Results: Of the 247 patients randomised, 82 patients were on prior LABA/ICS therapy. At Week 6, the proportion of patients who achieved the SAC-TDI score (≥1unit) was higher with QVA149 (39.5%) than placebo (19.0%; odds ratio [OR] 3.16) or tiotropium (20.0%; OR 3.31; both p<0.01). QVA149 significantly improved mean FEV_1 up to 4h post-dose and $FEV_1AUC_{0\text{-}4h}$ (table), and reduced mean daily rescue medication use (puffs/day) by 1.53 (p<0.001) and 0.44 (p=0.128) versus placebo and tiotropium, respectively.

Least squares mean treatment difference in FEV_1 and $FEV_1AUC_{0\text{-}4h}$, mL				
Time-points	QVA149 versus tiotropium		QVA149 versus placebo	
	Day 1	Week 6	Day 1	Week 6
FEV_1				
5 min	72	94	144	252
30 min	72	106	196	294
2 h	60	104	196	301
4 h	73	84	205	284
$FEV_1AUC_{0\text{-}4h}$	71	102	208	293
all p<0.05; $AUC_{0\text{-}4h}$, area under the curve from 0 to 4 hours; FEV_1, forced expiratory volume in 1 second				

Conclusions: Improvements in dyspnoea and lung function, and reduction in rescue medication use with QVA149 versus placebo and tiotropium have been shown in overall population.[1] Similar significant improvements were seen in subgroup population using LABA/ICS prior to study enrolment.

Reference: 1.Mahler et al. Eur Respir J 2014;43(6):1599–1609.

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ONCE-DAILY QVA149 IMPROVES DYSPNOEA, LUNG FUNCTION AND REDUCES RESCUE MEDICATION USE IN SYMPTOMATIC PATIENTS WITH COPD USING LAMA AS PRIOR MEDICATION: THE BLAZE STUDY

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Background: The BLAZE study reported the superiority of an approved dual bronchodilator, QVA149 (GOLD group B-D), in terms of improvement in self-administered computerised version of transitional dyspnoea index (SAC-TDI) total score and lung function versus placebo and tiotropium in patients with COPD[1]. Here, we present improvements in dyspnoea, lung function, and rescue medication use in the subgroup of patients on prior long acting muscarinic antagonist (LAMA) therapy.

Methods: In this blinded, double-dummy, 3-period crossover study, patients (with modified Medical Research Council dyspnoea scale grade ≥2) with moderate-to-severe COPD were randomised to once-daily QVA149 110/50 µg (via the Breezhaler® device), placebo or tiotropium 18 µg (via the HandiHaler® device).

Results: Of the 247 patients randomised, 115 were on prior LAMA therapy. Of these 115 patients, a higher proportion of patients on QVA149 reported ≥1unit improvement in the SAC-TDI total score (36.5%) versus placebo (16.4%; odds ratio [OR] 3.71; p<0.001) and tiotropium (20.2%; OR 2.51; p=0.007). At Day 1 and Week 6, QVA149 provided significant improvements in mean FEV_1 at all assessed time-points and FEV_1 $AUC_{0–4h}$ versus both placebo and tiotropium (table). QVA149 significantly reduced (p<0.001) mean daily rescue medication use (puffs/day) by 1.55 versus placebo and by 0.68 vs tiotropium.

Least squares mean treatment difference values of FEV_1 and FEV_1 AUC_{0-4h} (mL)				
	QVA149 versus placebo		QVA149 versus Tiotropium	
	Day 1	Week 6	Day 1	Week 6
FEV_1				
5min	126	271	65	97
30min	164	301	59	100
2h	206	310	59	112
4h	229	281	74	100
FEV_1 AUC_{0-4h}	205	305	63	111
All p<0.001 AUC_{0-4h}, area under the curve from 0 to 4 h; FEV_1, forced expiratory volume in one second				

Conclusion: In the subgroup of patients on prior LAMA therapy, QVA149 significantly improved SAC-TDI total score and lung function while also reducing rescue medication usage versus placebo and tiotropium.

Reference: 1. Mahler et al. Eur Respir J 2014; 43: 1599–1609

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DIFFERENCES BETWEEN PATIENTS WITH OVERLAP SYNDROME (COPD + OSAS) AND PATIENTS WITH OSAS

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Objective: To study the differences in symptoms, cardiovascular comorbidity, sleep respiratory parameters and of biochemical plasma measures between patients with COPD and obstructive sleep apnoea syndrome (OSAS) (overlap syndrome) and patients with only OSAS.

Material and Methods: 92 patients were included in the study. Patients were divided into two groups: overlap syndrome (n=43) and OSAHS (n=49).

The clinical characteristics and comorbidities were recorded. We performed a sleep study and plasma readings of haemoglobin, haematocrit, glucose, lipid profile, uric acid and C-reactive protein.

Results: By comparing the overlap group with the OSAHS group, we found the following significant differences:

1) Clinical: age (p<.015), neck circumference (p<.006), SpO_2 (p<.001)

2) Comorbidities: The overlap group had more cardiovascular risk factors (≥3) (p<.05), exsmokers and a greater history of ischaemic heart disease (p<.032). The OSAS-group were nonsmokers and active smokers (p<.001) and more dyslipidemia (p<.049).

3) Sleep study: the overlap group had a lower mean SpO_2 (p<.015) and higher CT90 (p<.03). In contrast, the OSAS group had longer apnoeic events (p<.003) and greater point drops in the desaturations (p<.001).

4) Biochemical measurements: The LDL values were higher in the OSAS group (p<.024), and the CRP values were higher in the overlap group (p<.046).

A correlation analysis of the patients in the overlap group there was a significant positive association between FEV_1 and the mean SpO_2 (r=0.373) and the minimum SpO_2 (r=0.386) in the sleep study. We also found a negative association with the duration of the apnoeic events (r=-0.41), age (r=-0.56).

Conclusions:

1) The patients with overlap syndrome have more cardiovascular comorbidity and greater systemic inflammation than those with only OSAS.

2) The patients with OSAH had longer apnoeic events and larger point drops in desaturation than the overlap patients.

3) We found a positive association between FEV_1 and the nocturnal oximetry values and a negative association with the duration of the apnoeic events.

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PREVALENCE OF VITAMIN D DEFICIENCY IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Objetives: To determine the prevalence of vitamin D deficiency in patients with COPD and analyze the relationship between plasma levels of vitamin D with clinical parameters, comorbidities and lung function.

Material and Methods: We included 70 patients (56 males and 14 females) diagnosed of COPD. Patients receiving treatment with vitamin D were excluded. We recorded some clinical variables (age, body mass index), pulmonary function (spirometry) and comorbidity using the Charlson index. Plasma levels of vitamin D, calcium and phosphorus were determined.

Results: The mean age of patients was 73 ± 9 years, BMI 27 ± 4 Kg/m^2. The average Charlson index was 1.9 ± 1.2. The distribution by air flow limitation was mild (15 patients, 20%), moderate (33 pt, 45%) and severe (22 pt, 30%). According to the GOLD classification: group A (33pt, 48%), group B (6pt, 9%), group C (5pt, 7%) and groupD (24pt, 35%).

The mean values of vitamin D were 18 ± 7ng/mL (their values were compared according to the season of the year), corrected calcium 9.6 mg/dL, phosphorus 3.3 mg/dL. The prevalence of vitamin D was 60% establishing as a cutoff <20 ng/dL. Differentiating three groups according to these levels: deficiency (<15 ng/dL): 27 pt (39%), insufficient (15-30 ng/dL): 38 pt (54%) and sufficient (> 30 ng / dL): 5 pt (7%) (p<0,0001).

We found that individuals with higher age, BMI, and higher comorbidity the levels of vitamin D were lower but not statistically significant. We also found no significant association between low levels of vitamin D in greater impairment of lung function.

Conclusion: The prevalence of vitamin D deficiency in patients with COPD is high. We found no statistically significant association between their plasma levels and lung function parameters.

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MICROBES AND MICROBIAL PRODUCTS IN CIGARETTE SMOKE. IMPLICATIONS FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE.

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Changes in the lung microbiome are involved in chronic obstructive pulmonary disease (COPD) exacerbations. Cigarette smoke is the best known risk factor for COPD. Health concerns of microbes in tobacco are starting to be acknowledged. Other groups showed that tobacco flakes inhaled from cigarettes could carry bacteria into the lungs. Moreover, bacterial products such as LPS remain in cigarette smoke and could contribute to inflammation. Our group is one of the first suggesting that Toll-like receptors (TLRs) are involved in the pathogenesis of COPD. TLRs are activated by microbial products. Our *in vitro* studies suggest that cigarette smoke induces inflammation partly via TLR9. TLR9 is activated by bacterial DNA.

Now we provided further evidence for a role TLR9 in the development of COPD. First, we demonstrated that chronic (5 weeks) activation of pulmonary TLR9 in mice leads to lung inflammation, emphysema, heart hypertrophy, and reduced airway function. Moreover, novel data were presented showing that not all bacteria are destroyed during tobacco burning. When smoke from burning cigarettes is passed over agar plates, colony-forming units clearly follow smoke deposition patterns unrelated to tobacco flake transmission.

Currently, a role for bioaerosol exposure in the development of COPD is still underappreciated. Our data emphasize that certain microorganisms and their products could become airborne during combustion. This information is relevant for (passive) smokers but also for women and children who use biomass for cooking indoors in developing countries. Better insight into cause could contribute to disease prevention and could open up new treatment strategies.

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OBESITY IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS UNDER HOME NON-INVASIVE VENTILATION

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Background: Chronic obstructive pulmonary disease (COPD) and obesity are disabling health conditions with increasing prevalence worldwide and can cause hypercapnic respiratory failure (HRF). Although obesity is a more prevalent comorbid condition in COPD patients, relatively little is known about how it may affect the evolution of HRF.

Non-invasive ventilation (NIV) is an effective treatment in obesity hypoventilation syndrome but the effectiveness of NIV for the treatment of HRF arising from stable COPD remains debatable.

Aim: To determine whether obesity affects the outcomes of COPD patients under home NIV.

Methods: This is a retrospective study that included for analysis COPD patients who received NIV between August 2011 and July 2014 at the Non-invasive Respiratory Care Unit of a university hospital. Demographic, anthropometric, functional respiratory parameters and follow-up data were collected. Obese (body-mass index ≥30 kg/m^2) and non-obese groups were compared.

Results: During this period 41 out of 109 COPD patients were obese (37.6%). The mean postbronchodilator FEV_1 percent-predicted (mean±SD) (46.5±14.4 *vs.* 33.8±13.1%, p<0.0001) and 6-min walk distance (287.6±77.7 *vs.* 230.5±79.5m, p<0.001) were significantly higher in obese COPD. Both groups had similar baseline daytime hypercapnia (obese: 52.0±7.0 *vs.* non-obese: 53.5±8.1mmHg, p>0.05).

The prevalence of obstructive sleep apnea syndrome (OSAS) was higher in obese (92.5%) *vs*. non-obese COPD patients (56.5%) (p<0.001).

Twenty-seven patients (24.8%) died during the 3-year follow-up with similar mortality in obese and non-obese patients (19,5% *vs*. 27,9%; p=0,32).

Although pressure support differed considerably between obese (14.4±4.4mmHg) and non-obese patients (18.3±6.4mmHg), with similar compliance (8.7±2.3 *vs*. 8.9±4.1h/day), daytime $PaCO_2$ decreased after home NIV was higher in obese patients (46.2±5.8 vs. 51.4±7.7mmHg, p<0.0001).

Conclusions: Obesity was a very frequent comorbidity in COPD patients under home NIV. Obesity is associated with other conditions such as OSAS that can be a confounding factor. More studies are needed to evaluate the interaction between COPD, obesity and OSAS. Are we facing "another overlap syndrome" or is obesity only an independent comorbidity of CODP?

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CHARACTERIZATION OF SPONTANEOUS AIRSPACE ENLARGEMENT IN MICE LACKING MICROFIBRILLAR-ASSOCIATED PROTEIN 4

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Background: Microfibrillar-associated protein 4 (MFAP4) is localized to extracellular matrix (ECM) fibers in blood vessels and the interalveolar septa of the lungs. Furthermore, it is present as a soluble protein in bronchoalveolar lavage. *Mfap4* has been previously suggested to be involved in elastogenesis in the lung.

Aim: We tested the prediction and aimed to characterize the pulmonary function changes and emphysematous changes that occur in *Mfap4* deficient (*Mfap4*$^{-/-}$) mice.

Methods: Invasive lung function measurements, micro-computed tomography (micro-CT), transmission electron microscopy (TEM), stereology

Results: Several *Mfap4*$^{-/-}$-dependent changes in lung parameters were detectable at 6 months and 8 months but not at 3 months of age in female mice. Significant changes included increases in total lung capacity and compliance, and a decrease in tissue elasticity characteristic of mild airspace enlargement. Using *in vivo* breath-hold gated micro-CT to assess 8-month-old *Mfap4*$^{-/-}$ mice, we found that the mean density of the lung parenchyma of the *Mfap4*$^{-/-}$ mice was decreased, and the percentage of low-attenuation areas was significantly increased by 14 %. TEM did not reveal apparent differences in the organization

of elastic fibers in the alveolar septa. Stereological analysis showed that the alveolar surface density in relation to the lung parenchyma and the total alveolar surface area inside of the lung were both significantly decreased in *Mfap4*$^{-/-}$ mice by 25 % and 15 %, respectively.

Conclusion: In conclusion, *Mfap4*$^{-/-}$ mice developed a spontaneous loss of lung function, which was evident at 6 months of age, and moderate airspace enlargement, with emphysema-like changes. The data did not support an essential role of MFAP4 in elastic fiber organization.

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PARK2-MEDIATED MITOPHAGY IS INVOLVED IN CIGARETTE SMOKE EXTRACT (CSE)-INDUCED CELLULAR SENESCENCE IN HUMAN BRONCHIAL EPITHELIAL CELLS (HBEC)

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Introduction: Cigarette smoke (CS)-induced mitochondrial damage with increased reactive oxygen species (ROS) production has been implicated in COPD pathogenesis by accelerating cellular senescence. Mitophagy may play a pivotal role for removal of CS-induced damaged mitochondria, and the phosphatase and tensin homolog (PTEN)-induced putative protein kinase 1 (PINK1)-PARK2 pathway has been proposed as a crucial mechanism for mitophagic degradation. Therefore, we sought to investigate to determine if PINK1-PARK2-mediated mitophagy is involved in the regulation of CS extract (CSE)-induced cell senescence and in COPD pathogenesis.

Methods: Mitochondrial damage, ROS production, and cell senescence were evaluated in primary human bronchial epithelial cells (HBEC). Mitophagy was assessed in BEAS-2B cells stably expressing EGFP-LC3, using confocal microscopy to measure colocalization between TOMM20 stained mitochondria and EGFP-LC3 dots as a representation of autophagosome formation. Mitophagy was also evaluated using electron microscopy in HBEC. To elucidate the involvement of PINK1 and PARK2 in mitophagy, knock down and overexpression were performed. PINK1 and PARK2 protein levels in lungs from patients were evaluated by means of lung homogenate and immunohistochemistry.

Results: CSE-induced mitochondrial damage was accompanied by increased ROS production and HBEC senescence. CSE markedly induced EGFP-LC3 dot formation with concomitant colocalization with TOMM20 in the presence of Bafilomycin A1, an autolysosome maturation inhibitor, suggesting that CSE treatment induces mitophagy. CSE-induced mitophagy was inhibited by PINK1 or PARK2 knockdown, resulting in enhanced mitochondrial ROS production and cellular senescence in HBEC. CSE-induced mitophagy was further confirmed by electron microscopic detection of autophagosomes with mitochondria inside. Evaluation of protein levels demonstrated decreased PARK2 in COPD lungs compared with non-COPD lungs.

Conclusion: These results suggest that PINK1-PARK2 pathway-mediated mitophagy plays a key regulatory role in CSE-induced mitochondrial ROS production and cellular senescence in HBEC. Reduced PARK2 expression levels in COPD lung suggest that insufficient mitophagy is a part of the pathogenic sequence of COPD.

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CORRELATION BETWEEN PATIENT PERCEPTION OF THE ABILITY TO PERFORM MORNING ACTIVITIES AND FINDINGS ON CLINICAL EXAMINATION IN COPD PATIENTS – BULGARIAN RELIEF STUDY

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Introduction: Patient reported outcomes facilitate the dialogue between the patient and their physician and represent important part of overall assessment of symptoms severity and contribute to the management of chronic obstructive pulmonary disease (COPD).

Objectives: This multi-center, prospective, non-interventional 12 weeks 4 visits study aimed to examine the possible correlation between the patient perceptions of their ability to perform morning activities and the clinician assessment of general health status in patients with group C and D COPD (GOLD Guidelines 2011) on combined therapy with inhaled corticosteroid/long acting ß$_2$-agonist (ICS/LABA).

Methods: Patient perception was assessed using total score of Capacity of Daily Living during the Morning (CDLM) self-reported questionnaire at baseline and 7 consecutive days per month in weeks 4, 8 and 12. Physicians' evaluation was performed using general health status visual scale at each visit. The correlation between CDLM total score and general health status score was investigated at every visit using the Kendall tau-b correlation test.

Results: The analysis of primary variables in 193 patients with full data found significant positive correlation on every visit: 0.3197 (visit 1), 0.3582 (visit 2), 0.3197 (visit 3) and 0.3922 (visit 4) of Kendall tau-b values ($p<.0001$ for all visits), implying a moderate positive connection between the 2 parameters.

Conclusions: The consistently positive correlation confirms that structured, written self-assessments shall be utilised in routine COPD management.

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QVA149 REDUCES THE RISK OF MODERATE-TO-SEVERE EXACERBATIONS COMPARED WITH OPEN-LABEL TIOTROPIUM IN PATIENTS WITH SEVERE COPD: THE SPARK STUDY

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Background: QVA149 is an approved once-daily (o.d.) dual bronchodilator combination of the long acting β2-agonist (LABA), indacaterol and the a long acting muscarinic antagonist (LAMA), glycopyrronium (GLY), for the maintenance treatment of patients with symptomatic COPD. Here we present the results of a post-hoc analysis conducted to evaluate the rate ratio (RR) of exacerbations in patients with severe COPD in the SPARK study.

Methods: This 64-week, multicentre, double-blind, parallel-group, active-controlled (open-label TIO and GLY) study randomised patients with severe-to-very severe COPD and a history of ≥1 exacerbation in the previous year to receive o.d. QVA149 110/50µg, GLY glycopyrronium 50 µg or TIO tiotropium 18 µg.

Results: Of the 2224 patients randomised, 1744 had severe COPD (QVA149=579; glycopyronium=584; tiotropium=581). QVA149 reduced the risk of moderate-to-severe exacerbations vs. glycopyrronium by 11% (RR 0.89; 95% CI 0.77, 1.04) and tiotropium by 15% (RR 0.85; 95% CI 0.73, 0.98) in patients with severe COPD. In a majority of subgroups QVA149, compared with tiotropium, reduced the risk of moderate-to-severe exacerbations (Figure). A similar reduction in risk of moderate-to-severe exacerbations was also seen with QVA149 compared with glycopyronium in most of the subgroups.

Conclusions: Risk of moderate-to-severe exacerbation was reduced in severe patients with COPD who were treated with QVA149 compared with glycopyrronium and tiotropium

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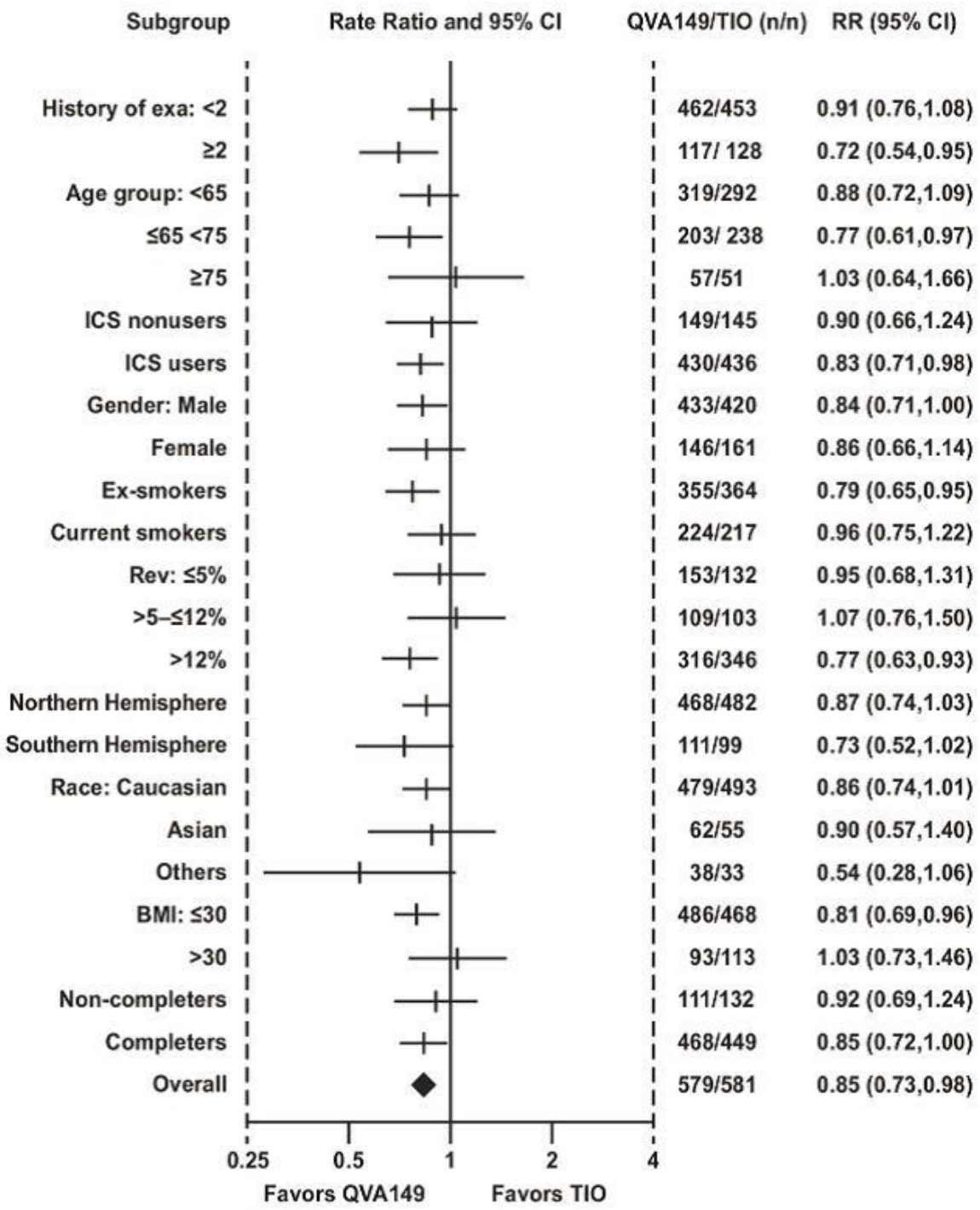
Figure: Rate ratio of moderate to severe exacerbations in QVA149 treated patients compared with TIO treated patients.



CI, confidence interval; TIO, tiotropium; RR, rate ratio; exa., exacerbations; Rev., FEV_1 reversibility; BMI, body mass index

BURDEN OF DYSPNEA IN COPD: IMPACT ON HEALTH STATUS AND ACTIVITY IMPAIRMENT

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Rationale: Individuals treated for chronic obstructive pulmonary disease (COPD) may continue to suffer from symptoms. Dyspnea is recognized as particularly bothersome, and patient-reported severity of dyspnea is used as part of the patient classification system developed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD). We aimed to assess the burden of dyspnea among patients being treated for COPD using patient-reported outcomes.

Method: Data came from the 2013 5EU National Health and Wellness Survey (N=62,000). All measures were self-reported. Respondents were included if they were ≥40 years old and reported currently taking a prescription medication for COPD, emphysema, or chronic bronchitis; those reporting diagnosis of asthma were excluded. Outcome measures were the Short Form-36 questionnaire (SF-36v2), Work Productivity and Activity Impairment questionnaire, and self-reported healthcare use in the past 6 months. Respondents were categorized into lower- and higher-dyspnea groups using an item similar to the modified Medical Research Council (mMRC) scale and the GOLD categorization (mMRC levels 0-1 vs. ≥2). These groups were compared using t-tests for continuous variables and chi-square tests for categorical variables.

Results: A total of 768 respondents were included, 245 (32%) of whom were in the high-dyspnea group. There were no statistically significant differences between the groups in any of the baseline or demographic characteristics. Relative to the lower-dyspnea group, the higher-dyspnea group had notably worse mean mental and physical component summary scores of the SF-36v2, lower health utility scores, and a higher level of health-related impairment in daily activities. These individuals also reported a greater number of visits to pulmonologists and respiratory therapists in the prior 6 months (Table).

Table: Health outcomes by level of dyspnea

	Level of Dyspnea (mMRC Equivalent)				
	Lower (0-1) (n=523)		Higher (≥2) (n=245)		
	Mean	SD	Mean	SD	p-value
Physical component summary	43.3	9.3	34.9	8.7	<.001
Mental component summary	45.0	12.1	40.8	12.0	<.001
Health utility score (SF-6D)	0.64	0.12	0.57	0.10	<.001
Activity impairment (%)	42.3	31.3	64.8	27.1	<.001
Pulmonologist visits (past 6 months)	0.3	0.7	0.7	1.2	<.001
Respiratory therapist visits (past 6 months; $n_{(0-1)}$=453; $n_{(\geq 2)}$=206)	0.1	0.3	0.2	1.0	.001

Conclusions: Despite treatment, many COPD patients experience breathlessness. These individuals show large and meaningful decrements in health-related quality of life relative to other patients despite similar sociodemographic characteristics. More effective treatment of dyspnea may provide substantial benefit to patient well-being. Higher self-reported dyspnea is associated with a significant burden in health outcomes.

Funding: Novartis-AG

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THE EFFECT OF A DIETICIAN-LED OUTPATIENT CLINIC ON HOSPITAL ADMISSIONS FOR EXACERBATION IN COPD PATIENTS WITH A LOW BODY MASS INDEX (BMI)

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A recent meta-analysis revealed nutritional support improves respiratory muscle strength, hand grip strength and exercise performance in COPD patients.[i] Hand grip strength is a useful predictor of hospital admission rate and length[ii], but the literature is scarce when correlating weight change in COPD patients with hospital admission rate and or length.

A novel respiratory specialist dietician led outpatient service was initiated for COPD patients with a low BMI (<20), who are often not able to partake in pulmonary rehabilitation courses. Patients were advised about their diet and prescribed oral nutritional supplements. They were reviewed every three months in the outpatient setting.

Objectives:

1. To determine whether an outpatient dietician-led intervention was effective in improving patient's body weight.
2. To determine whether weight gain was related to fewer rates and/or duration of hospital admission.

Methods: The medical notes from twenty COPD patients who underwent outpatient nutritional intervention were reviewed to gather data on weight change; rate and length of hospital admissions for COPD exacerbation. The patients were either referred to the outpatient service from their general practitioner or whilst an inpatient in hospital.

Results: Eleven patients gained weight with the nutritional intervention. Eleven patients had fewer hospital admissions within one year after the intervention, compared to one year prior (55%). Of these, 8 patients had gained weight (72%). The median length of hospital stay was 4 days (1 – 60 days) prior to the dietetic intervention compared to 2 days (1 – 20 days) post intervention.

Conclusion: This small study suggests that dedicated outpatient led nutritional support may reduce both hospital admission rate and length of stay in COPD patients with a low BMI.

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ENGAGING PATIENTS WITH E-CLINICAL TECHNOLOGY: INCORPORATING PATIENT PREFERENCES INTO COPD CARE AND CLINICAL TRIALS

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Background/Aims: An important characteristic of successful healthcare and patient participation in clinical trials is strong communication between patients and their providers. Using e-clinical technology can be one mechanism for achieving this goal. We propose that the optimal implementation considers patient preference and ease of use, and that incorporating e-clinical technology can lead to increased patient compliance and ultimately translate into improved clinical care.

Methods: We surveyed 100 patients in the U.S. with COPD; questions focused on mobile technology use, perceptions, and preferences.

Results: Patients ranged in age from 34 to 86 years and were 55% female. 39% owned a smartphone and 41% reported using the internet daily or weekly. 82% of patients reported interest in using electronic methods to interact more with their physician between visits to help manage and treat their disease. When asked about the most effective way of improving their health and managing their disease, 38% of patients responded "increasing communication and interactions between my physician and me" and another 30% were interested in monitoring and tracking their disease, symptoms, and/or medications electronically on a regular basis so that their physician could see their health status in real time. Patients preferred electronic methods of managing their disease, including email and text message communications with providers, clinical visit scheduling via smartphone, and medication reminders via smartphone.

Conclusions: Patients with COPD are interested in using electronic methods to increase communication with their physician and manage their disease. Most patients in this survey did not own a computer and rarely used email, but many reported using text messaging frequently. Text messaging can be used for medication reminders, visit scheduling, and/or direct physician communications. Providers should consider engaging COPD patients with e-clinical technology to increase patient-physician communication and enable them to manage their disease.

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INFLUENCE OF SMOKING AND COPD TO LUNG FUNCTION IN PATIENTS WITH PULMONARY TUBERCULOSIS WITHOUT CAVITIES.

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Pulmonary tuberculosis (PT) and COPD both are significant social problems. Association between smoking, COPD and PT is often under estimated. Most of patients with PT are smokers and may often have co-morbidty as COPD.

Aims: to evaluate the effect of smoking and COPD on outcomes of pulmonary function in patients with PT without cavities and duration of tuberculosis till 1 year.

Methods: 82 patients with PT with infiltrates in 1-3 segments without cavities and disease duratuion till 1 year are examined. 1 group - 35 non-smokers, 2 - 29 smokers without signs of COPD (9,0 pack-years of smoking, 95% CI 3,7-14,3), 3 - 18 patients with COPD (37,8 pack-years, 95% CI 19,3-56,2). We used spirometry, bodyplethysmography, measurement of diffusion capacity for carbon monoxide by single breath method (DLCO) on MasterScreen Body Diffusion (VIASYS healthcare), Computed tomography on TOSHIBA AQUILION 32. We used descriptive statistics and Spearman correlation analysis (Statistica, statSoft Inc., USA).

Results: There were not significant ventilation disorders in groups 1 and 2. DLCO was moderately decreased in both groups. But only non-smokers had significantly more DLCO vs patients with COPD (78,7±11,2 vs 66,7±11,3, $p<0,05$). DLCO in smokers and COPD patients was not significantly different (74,4±11,7 vs 66,7±11,3, $p>0,05$). There was an increase in hemoglobin from group 1 to 3 (12,8; 14,2; 15,2; $p<0,01$ gr. 1 and 2, gr. 1 and 3). The correlation analysis revealed an association between DLCO, air trapping volume, Hb and the pack-years of smoking (-0,41; 0,37; 0,45; $p<0,05$).

Conclusions: There were not significant ventilation disorders in patients with PT without cavities and disease duration till 1 year without COPD. The patients who had the association COPD and PT had most significant decrease of DLCO, but mean value of DLCO in smokers and COPD patients was not significantly different. DLCO decreasing was associated with the pack-years of smoking. Patients who smoke should be encouraged ti quit or smoke less to achieve a better outcome.

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CLINICAL PRESENTATION AND PROGNOSIS OF PNEUMONIA IN CHRONIC LUNG DISEASE

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Introduction: Chronic obstructive pulmonary disease (COPD) and asthma are frequent comorbidities in patients with community-acquired pneumonia (CAP). However, the impact of chronic lung diseases on outcome in CAP is not well established.

Methods: We prospectively studied the clinical presentation of 370 patients admitted in our clinic with CAP during a 4-yr period. Demographic, clinical, laboratory, microbiological and progress variables were collected. A comparative analysis of disease severity and course between the three groups of patients - asthma, COPD, control - was performed.

Results: Of 370 cases of CAP, with a mean age 63,4 ± 18 years, 111(30%) patients have COPD and 31(8%) were asthmatics. Patients with asthma were younger (<35 years : 18%(asthma) vs. 1% (COPD) vs. 13%(control), p<0,001) and mostly women (71% vs. 32% vs. 50%, p<0,001). COPD patients presented less often with fever (100% vs.**75%** vs. 92%,p <0,001) and pleuritic pain (35% vs. **18%** vs. 34%, p=0,008) comparing to non-COPD patients. Additionally, they were more hypoxemic (PO2 <60 mmHg) (70% vs. **86%** vs. 59%,p<0,001) and categorized in higher CURB65 class (1,5 vs. **2,4** vs. 1,7; p<0.001) compared with non-COPD patients(figure 1). Regarding therapy asthma and COPD patients received more often quinolones (**56%** vs.51% vs.

38%,p=0,028) and asthma pts more often cortcoids comparing to the non-asthmatics ones (**57%** vs.38% vs. 16%, p<0,001). In-hospital mortality was higher in the asthma patients (**11%** vs. 6% vs. 5% p =0.036); although the complication rate was similar between the three groups of patients.

Conclusion: Although, COPD patients presented with more severe clinical picture, asthmatics had a higher mortality rate in our study. This happens possibly because of the higher awareness of general practitioners while treating patients with COPD, the decreased incidence of pulmonary complications and the lack of maintenance therapy with inhaled steroids in all the asthmatics of our study.

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COMORBIDITIES AND CAUSE-SPECIFIC MORTALITY IN MILD CHRONIC OBSTRUCTIVE PULMONARY DISEASE: THE ROTTERDAM STUDY

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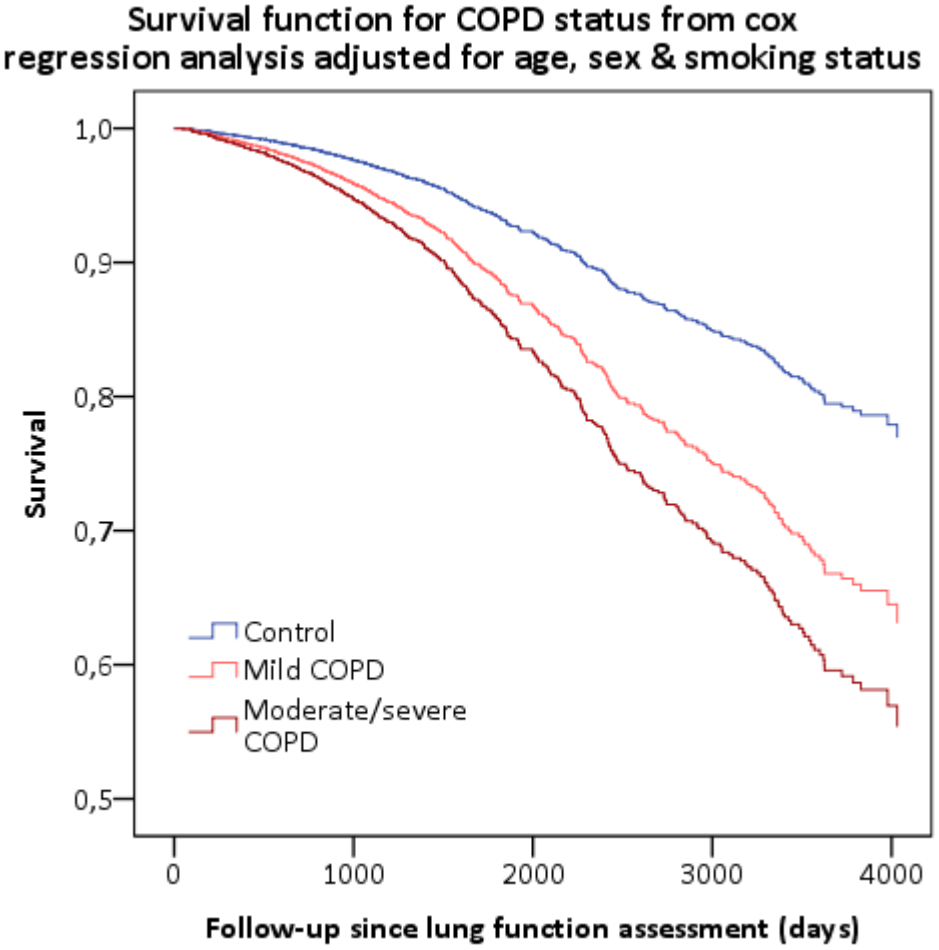
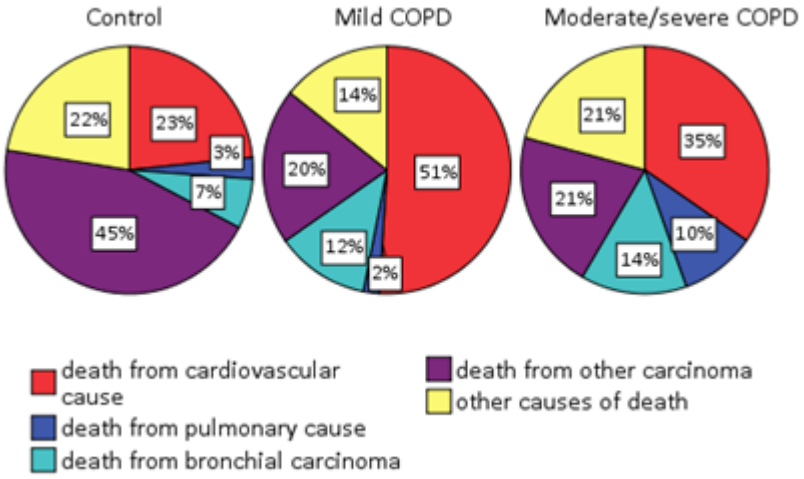
Background: Since patients with mild chronic obstructive pulmonary disease (COPD) are rarely included in large COPD cohort studies and clinical trials, little is known about their comorbidities and causes of death.

Aim: To identify the main causes of death in subjects with mild COPD (GOLD stage I)[1] compared to moderate/severe COPD and subjects with normal spirometry without respiratory symptoms.

Methods: Within the Rotterdam Study, a large prospective population-based cohort study, information on vital status was obtained regularly from the municipal health authorities in Rotterdam. The cause of death was determined in 257 participants who had performed a spirometry at the research centre between 2002 and 2010. The classification of deaths was based on the 10th revision of the International Classification of Diseases (ICD-10)[2].

Results: Subjects with mild COPD are at high risk of dying.(Figure 1 adjusted for age, sex and smoking) However, of the subjects with mild COPD who died, two thirds of deaths were attributable to cardiovascular causes (51%) or lung cancer (12%), whereas only 2% were attributable to pulmonary causes.(Figure 2)


Survival function for COPD status from cox regression analysis adjusted for age, sex & smoking status
1,0
0,9
0,8
0,7
0,6
0,5
Survival
Control
Mild COPD
Moderate/severe COPD
0
1000
2000
3000
4000
Follow-up since lung function assessment (days)


Control
Mild COPD
Moderate/severe COPD
22%
23%
3%
7%
45%
14%
20%
51%
12%
2%
21%
35%
21%
10%
14%
death from cardiovascular cause
death from other carcinoma
other causes of death
death from pulmonary cause
death from bronchial carcinoma

Conclusion: The high percentages of cardiovascular death and lung cancer death emphasize the need for optimal diagnosis and treatment of comorbidities in patients with mild COPD to decrease mortality.

[1] The diagnosis of COPD was based on an obstructive spirometry examination according to the modified Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [proportion of the forced vital capacity exhaled in the first second (FEV1/FVC) < 0.7] and classified into mild or moderate/severe by forced expiratory volume in one second (FEV1)% predicted of ≥ 80% and < 80% respectively.

[2] International statistical classification of diseases and related health problems, 10th revision. Geneva: WHO, 1992.

Conflict of Interest: No commercial funding sources are involved, authors have no commercial interests relevant to this topic.

Funding: This study was supported by the Fund for Scientific Research Flanders (FWO) project G035014N.

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RELATIONSHIP BETWEEN THE PRESENCE OF BRONCHIECTASIS AND FREQUENT EXACERBATION IN THAI COPD PATIENTS

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Background: COPD exacerbation in the past years is significant risk factor for future exacerbation. Bronchiectasis overlapped COPD phenotype attenuates disease severity and future risk.

Objective: We hypothesized whether bronchiectasis is associated with frequent COPD exacerbations. Bacterial and mycobacterial airway infection were examined as underlying of bronchiectasis in Thai COPD patients.

Materials and methods: Cross sectional study in COPD patients was conducted in 2013-2014. History of COPD exacerbations and hospitalizations were reviewed. Spirometry and HRCT of chest during stable phase were performed. Symptoms were assessed by using CAT score and mMRC. Isotonic saline was used via ultrasonic nebulization for sputum induction. Specimens were processed for microbiology.

Results: Total 72 patients were recruited and mean age 72.4 years. GOLD A, B, C and D were noted in 20%, 27.1%, 14.3% and 38.6% of patients. The frequent exacerbation (≥ 2/year) and/or at least one hospitalization in the past year were noted in 40.28%. Median CAT scores of COPD with frequent and non-frequent exacerbation were 20.5 vs. 11 (p 0.004). Bronchiectasis was detected in 34 cases (47.2%). CAT score of COPD with and without bronchiectasis was not different (p 0.49). FEV_1% of frequent COPD exacerbators and non-frequent exacerbators were 51.7% vs. 65.4% (p 0.007). FEV_1% of COPD with and without bronchiectasis were 59.8% vs. 60.4% (p 0.9). The significant association between bronchiectasis and frequent COPD exacerbation and/or COPD related hospitalization was noted (p 0.038). Odd ratio of bronchiectasis for the frequent or severe exacerbation was 2.76 (95% CI: 1.04-7.29, p 0.041). Bacterial and mycobacterial growth were identified in 12.5 % and 11.1 % of sputum specimens. Neither positive aerobic nor mycobacterial culture was associated with bronchiectasis or frequent COPD exacerbation.

Conclusions: The prevalence of HRCT detected bronchiectasis in COPD is common. Bronchiectasis is associated with the frequent exacerbations or hospitalizations in the past year. Physiologic derangement is similar between COPD with and without bronchiectasis. Mycobacterial infection in Thai COPD with bronchiectasis is uncommon.

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BENEFITS OF SELF-MANAGEMENT EDUCATION IN COPD EXACERBATIONS

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Background: There is emerging evidence that disease management with self-management education programs, provided by a case manager might benefit COPD patients. The objective of the present study was to examine the effect of a structured self-management education program including treatment with prednisolone and antibiotics in case of exacerbation in COPD. The overall goal was to reduce frequency of hospitalizations associated with acute exacerbations and enhance the quality of life for the patients.

Subjects and Methods: From April 2010 to May 2013 a total of 134 patients were included in the study. Patients were educated in the recognition and self-treatment of acute exacerbations by a home-visiting experienced COPD-nurse at 1, 3, 6 and 12 months (intervention period) after discharge from the hospital's pulmonary department. After the intervention period, the patients were followed for one year (follow-up period) with registration of acute exacerbations and hospitalizations.

Results: Among the 134 included patients, 90 participated in the one-year intervention period, by May 2013 50 patients had completed the one-year follow-up period. Among the 50 patients, there was a significant reduction in the total number of hospitalizations due to COPD. In the year prior to inclusion (pre-inclusion period), the 50 patients had 67 hospitalizations due to acute exacerbations. In the intervention period hospitalizations dropped to 37 and in the follow-up period they showed a further decline to 26 (total reduction of 61%) ($p < 0.001$). The number of self-treatments increased from an average of 2.6 in the pre-inclusion period to 3.3 in the intervention period and declined to 2.6 in the follow-up period. During the study no significant changes were observed in FEV1%-predicted, MRC-score, BMI, CAT-score or CCQ-score.

Conclusions: The present study shows that this particular self-management education of COPD patients, given by a COPD-nurse, reduces frequency of hospitalizations associated with acute exacerbations and apparently enhances quality of life for patients. Taken all together this approach to COPD treatment presumably also is cost-effective.

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CORRELATION BETWEEN EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND METABOLIC SYNDROME

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Background/Aims: Systemic inflammation has been considered to be the underlying mechanism in pathogenesis of chronic obstructive pulmonary disease (COPD) and metabolic syndrome (MetS).

The aim of study was to evaluate the correlation between exacerbations of COPD and MetS.

Methods: A total number of 92 patients with COPD were included in retrospective study during 12 months follow-up, which medical recorsd with pulmonary function tests, chest X-rays ant laboratory tests results were analyzed. Patients were divided into two groups, 34 with Mets and 58 without.

Metabolic syndrome was defined using criteria of the World Health Organisation.

The exacerbations of COPD was defined according to the GOLD guidelines.

Results: MetS was present in 37% of the COPD patients. The frequency of patients with exacerbations of COPD among those with MetS was 38%, and among those without MetS was 19%.

There was statistically significant difference ($p<0,05$) in number of subjects with exacerbations of COPD between the group of patients with MetS and the group without it.

However, there was no statistically significant difference ($p>0,05$) in the increse level of serum CRP during exacerbations of COPD between patients with and those without MetS.

Conclusions: The study demonstrated a correlation between exacerbations of COPD and MetS.

Having regard the role of cytokines in its pathogenesis, the systemic inflammation may be considered as a common basis and linkage between the two conditions.

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EFFECTS OF CORTICOSTEROID THERAPY ON THE DEVELOPMENT OF OSTEOPOROSIS IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Background/Aims: One of the most obvious causes of osteoporosis in the patients with chronic obstructive pulmonary disease (COPD) is treatment with corticosteroids, both as systemic (SCsTh) and as inhaled (ICsTh) therapy.

The aim of the research was to determine the existence of correlation between the use of corticosteroid therapy in treatment of patienst with COPD and developement of osteoporosis in these patients.

Methods: Data were retrospectively collected by analyzing of medical records of 71 COPD patients, all females in postmenopausal age, smokers, who owned the results of the dual-energy X-ray absorptiometry (DXA) scan.

Observed population included 43 COPD patients on corticosteroid therapy, divided into two groups. First group consisted of 12 patients on SCsTh, and the second one of 31 patients on ICsTh.

Control group included 28 COPD patients without corticosteroid therapy.

Results: Prevalence of osteoporosis among COPD patients was 34%. In observed population it was 49%, in group on SCsTh 75% and in group on ICsTh 19%. Prevalence of osteoporosis in control group was 11%.

The results have shown that there was no statistically significant difference in prevalence of osteoporosis between groups of COPD patients on SCsTh and on ICsTh ($p>0,01$), but there was statistically significant difference between observed population and control group ($p<0,01$).

Also, there was statistically significant difference in prevalence of osteoporosis between group on SCsTh and control group ($p<0,01$).

Statistically significant difference in prevalence of osteoporosis was between group on ICsTh and control group, only at the level of safety of 95%, but not at the level of safety of 99%.

Conclusions: Study demonstrated that the prevalence of osteoporosis among COPD patients was associated with the use of corticosteroid therapy.

Furthermore it would be important to consider in detail the advantages of inhaled over the systemic corticosteroid therapy, bearing in mind not so convincing difference in prevalence of osteoporosis among COPD patients on ICsTh compared to COPD patients without corticosteroid therapy.

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EXHALED NITRIC OXIDE AS A BIOMARKER IN COPD PATIENTS REGARDING THE SMOKING STATUS

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Objective: Airway inflammation plays an important role in the pathogenesis of COPD. FeNO has been identified as a valuable inflammatory biomarker in varuious respiratory diseases, including COPD. It was showed that cigarette smoking can influence the level of FeNO.

The aim of our study was to assess the FeNO level in COPD patients depending on their smoking status, since cigarette smoking is a frequent habit of those patients.

Methods: FeNO and lung function were measured in two groups of patients with clinically stable COPD, 20 current smokers and 20 ex-smokers. The ex-smoker group was formed by patients who have quit smoking for at least 1 year.

Result: There were no differences between smoking and ex-smoking groups in age (mean 66.1 vs. 67.7 years, p=0.2867), FVC (mean 72.7 % of predicted vs.69.46 % of predicted, p=0.2333), FEV1 (mean 51.8% of predicted, 42.2 % of predicted, p=0.9674). FeNO was significantly lower in smokers (6.89 ppb) compared to ex-smokers (11.0 ppb) (p=0.0052). There was no significant correlation between FEV1 and FeNO in both groups of patients.

Conclusion: Our results show that the concentration of exhaled NO is significantly lower in smoking COPD patients. Due to the negative influence of cigarette smoke on levels of exhaled NO, attention should be paid on smoking habit when inflammatory status is assessed by FeNO measurement in COPD.

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IMPACT OF WALKING PRESCRIPTION ON THE EFFECTS OF PULMONARY REHABILITATION IN COPD PATIENTS WITH HIGH BODY MASS INDEX.

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Background/Aim: Chronic obstructive pulmonary disease (COPD) patients with high body mass index (BMI) are less physically active compared to COPD patients with normal weight and age matched healthy population. Although there is a growing prevalence of weight excess in COPD patients, the precise effects of pulmonary rehabilitation (PR) on exercise endurance, physical activity (PA) and quality of life (QOL) in those patients remain unclear. We evaluated the combined effects of walking prescription and pulmonary rehabilitation on exercise endurance, PA and QOL in COPD patients with high BMI.

Methods: We conducted a retrospective analysis on the data of 32 consecutive COPD patients [FEV1: 63.06 (21.2) %] with high BMI [30.94(5.089)] who had completed 8 weeks outpatient pulmonary rehabilitation. All patients received 30 mins supervised exercise training for 3 session and 1 hour of self management education for 2 sessions per week. A baseline walking prescription of 80 % average of their initial 6MWT was prescribed for 4-5 days per week in physical activity log (PAL). Baseline and post rehabilitation outcomes include Body Mass Index (BMI), 6 min walk test (6MWT), PAL, COPD Assessment Test (CAT), Borg scale, Modified Medical Research Council dyspnoea scale (MMRC) and Chronic Respiratory Disease Questionnaire (CRDQ).

Results: Significant difference was observed in PA, exercise endurance, dyspnoea and QOL. In addition, there was a significant co-relation between BMI and PA pre and post PR.

Conclusion: This study supports a need for a walking prescription to be incorporated in pulmonary rehabilitation to improve PA in COPD patients with high BMI.

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GLYCOPYRRONIUM ONCE-DAILY SIGNIFICANTLY IMPROVES LUNG FUNCTION AND HEALTH STATUS WHEN CO-ADMINISTERED WITH FIXED DOSE COMBINATION OF FLUTICASONE/SALMETEROL IN PATIENTS WITH COPD: THE GLISTEN STUDY

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Background: The GLISTEN trial studied triple therapy - long-acting muscarinic antagonist added to fixed-dose combined inhaled corticosteroid and long-acting β_2-agonist - in Chronic Obstructive Pulmonary Disease.

Methods: GLISTEN was a randomised blinded placebo controlled trial in patients with moderate to severe Chronic Obstructive Pulmonary Disease comparing glycopyrronium 50 µg, tiotropium 18 µg or placebo (each once-daily), when administered with fixed dose combination of fluticasone/salmeterol 500/50 µg twice daily. The primary objective was to determine non-inferiority of glycopyrronium versus tiotropium (added to fluticasone/salmeterol) on trough FEV_1 after 12 weeks. An important secondary aim was to demonstrate the superiority of triple therapy compared to fluticasone/salmeterol treatment alone.

Results: A total of 773 patients (mean age 68 years; post-bronchodilator FEV_1 57.2% predicted) were randomised; 84.9% completed the study. At week 12, glycopyrronium demonstrated non-inferiority to tiotropium when added to fluticasone/salmeterol for trough FEV_1: least square mean treatment difference -7mL (Standard Error [SE] 17.4). There were statistically and clinically significant improvements in trough FEV_1 at Week 12 with glycopyrronium added to fluticasone/salmeterol versus fluticasone/salmeterol alone (LSM difference 101mL, $p<0.001$). Glycopyrronium (administered with fixed dose combination of fluticasone/salmeterol) produced statistically significant improvement in health status after 12 weeks versus fluticasone/salmeterol alone (St. George's Respiratory Questionnaire total score least square mean treatment difference -2.154, $p=0.02$). Glycopyrronium (administered with fixed dose combination of fluticasone/salmeterol) also demonstrated significant reduction in rescue medication use versus fluticasone/salmeterol alone (least square mean treatment difference -0.72 puffs/day; $p<0.001$). The incidence of adverse events (58.4%, 64%, 57.6%) and serious adverse events (5.8%, 8.5%, 5.8%) was comparable between glycopyrronium, tiotropium and placebo (added to fluticasone/salmeterol), respectively.

Conclusion: Compared to fluticasone/salmeterol fixed dose combination alone, glycopyrronium 50 µg co-administered with fluticasone/salmeterol fixed dose combination demonstrated significant improvements in lung function, health status and rescue medication use across a range of COPD severities in patients with minimal history of exacerbations.

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POCO-POCO-DANCE THERAPY IMPROVES QUALITY OF LIFE AND EXERCISE TOLERANCE OF COPD PATIENTS

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Introduction: Pulmonary rehabilitation program has been a primary management among COPD patients to optimize physical performance and health status. To ensure active participation, the exercise programs should be enjoyable and pleasurable. Dance therapy can be enjoyable and pleasurable with physical and psychological benefits to promote participation and adherence. Poco-poco dance is a common cultural dance among Malaysian elderly to improve physical performance.

Objective: This study evaluates the effects of poco-poco dance therapy intervention program on health related quality of life (HRQoL) and exercise tolerance compared to the traditional pulmonary rehabilitation program in a local hospital in Malaysia. The intervention was carried out twice per week for 8 weeks duration as an out-patient program following ethical approval.

Methods: This is a quasi-experimental study involving a control group (CG) with the usual pulmonary rehabilitation program and an intervention group (IG) with poco-poco dance therapy. There were 12 participants in CG and 11 in CG with mean age of 63.5 ± 8.0 years and 64.6 ± 10.7 years respectively.

Results: SPANOVA analysis demonstrated significant within-subjects effect (p<0.005) in 6 minute walk tests (6MWT) and Borg scale indicating improved exercise tolerance more so in IG (347.64 ± 70.66m) compared to CG(333.17 ± 82.44m). The quality of life as measured by SGRQ showed no significant interaction effect in all four domains. The within-subjects effect (symptom -0.335; activities -0.743; impact -0.620; total score -0.861) and between-subjects effect (symptom -0.835 ; activities -0.416; impact-0.397 ; total score -0.513) suggest the quality of life of both groups improves with no significant differences observed (p>0.05) between the groups.

Conclusions: Poco-poco dance therapy could be an alternative adjunct of physical activity for COPD patients integrated as a component of pulmonary rehabilitation program to improve physical performance and health status.

Key Words: pulmonary rehabilitation program; dance therapy, COPD, quality of life, exercise tolerance

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IDENTIFICATION OF LUNG MECHANICAL PROPERTIES IN PATIENTS WITH ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (AECOPD) OR ACUTE HEART FAILURE (AHF) THROUGH FORCED OSCILLATION TECHNIQUE (FOT): PRELIMINARY RESULTS

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Background: Differentiating between AECOPD and AHF in patients with acute dyspnea represents an important clinical issue in patients with acute dyspnea. Nowadays there are no accurate methods capable of discriminating the two diseases. Our hypothesis is that FOT allows to identify the different mechanical properties of AECOPD and AHF.

Methods: During the first day of hospitalization each patient underwent two FOT measurements in multifrequency (5-11-19 MHz) for two minutes at tidal volume in a sitting position. Three groups were evaluated: 11 patients with AECOPD (1 woman, age 69±8 years, mean±SD, BMI 24,5±2,7 kg/m², FEV1 35±17% predicted, all smokers or ex); 11 patients with AHF, NYHA IV class (5 women, age 75±1, BMI 29,4 ± 8,1 kg/m², 5 smokers or ex) and 6 healthy non-smoker subjects (3 women, mean age 63±3, BMI 27,7±5,0 kg/m², normal spirometry).

Results: All 28 subjects executed FOT with adequate compliance. 5-Hz resistance and reactance, 11 and 19-Hz reactance values were significantly increased in AECOPD compared to the other two groups (P<0,05). 11 and 19-Hz resistance values did not show significant differences between the three groups. Expiratory flow limitation (ΔXrs >2,81 cmH_2O*s*L^{-1}) distinguished AECOPD from the other two groups (P<0,05).

	Control	*AECOPD*	*AHF*	*pANOVA*
R 5-Hz	2,30±0,88*	5,90±4,12	3,27±1,76*	**0,035**
X 5-Hz	-1,11±0,75*	-4,16±3,88	-1,37±1,46*	**0,031**
R 11-Hz	2,16±0,78	4,23±2,68	2,88±1,36	0,098
X 11-Hz	-0,20±0,18*	-2,61±2,30	-0,74±0,92*	**0,008**
R 19-Hz	1,98±0,79	3,21±2,08	2,41±1,16	0,265
X 19-Hz	0,49±0,23*	-1,47±1,44	-0,12±0,60*	**0,001**
ΔXrs	-0,24±0,20*	3,39±4,21	0,67±1,76*	**0,033**

*****p<0,05 significant mean difference with AECOPD group

R=total resistance (inspiratory and expiratory), cmH_2O*s*L^{-1} mean±SD

X=total reactance (inspiratory and expiratory), cmH_2O*s*L^{-1} mean±SD

ΔXrs=expiratory flow limitation cmH_2O*s*L^{-1}

Conclusion: These results suggest that FOT may permit accurate discrimination of AECOPD from AHF in hospitalized subjects with acute dyspnea, and should therefore be confirmed on a larger scale.

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CHRONIC OBSTRUCTIVE PULMONARY DISEASE IS ASSOCIATED WITH AN INCREASED RISK OF PERIPHERAL ARTERIAL DISEASE

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Background: Chronic obstructive pulmonary disease (COPD), peripheral arterial disease (PAD) and ischemic heart disease are considered to be a smoking-related triad. However, only a few studies investigated the relationship between COPD and PAD using limited study sample. We aimed to examine the risk of PAD among patients with COPD using a nationwide cohort database inTaiwan**.**

Methods: We conducted a retrospective cohort study using data from the National Health Insurance system of Taiwan. The COPD cohort included 361,023 patients who were newly diagnosed and recruited between 1998 and 2008. Each patient with COPD was randomly frequency-matched with two participants without COPD on age, sex, and the year of index date. The newly diagnosis of PAD was followed up until the end of 2010. The relative risks of PAD were estimated using Cox proportional hazard models after adjusting for age, sex, index year and comorbidities.

Results: The overall incidence rate of PAD was 2.34–fold greater in the COPD cohort than in the non-COPD cohort (3.71 vs. 1.58 per 1000 person-years). Further analyses indicated that the risk ofPAD was higher in males, individuals younger than 50 years, and without comorbidity among the subgroups.

Conclusion: This nationwide population-based study indicates that the incidence of PAD is significantlyhigher in patients with COPD than in those without COPD and the hazard ratio was especiallyhigh in younger patients. Therefore, regular examination for PAD in patients with COPD may be considered.

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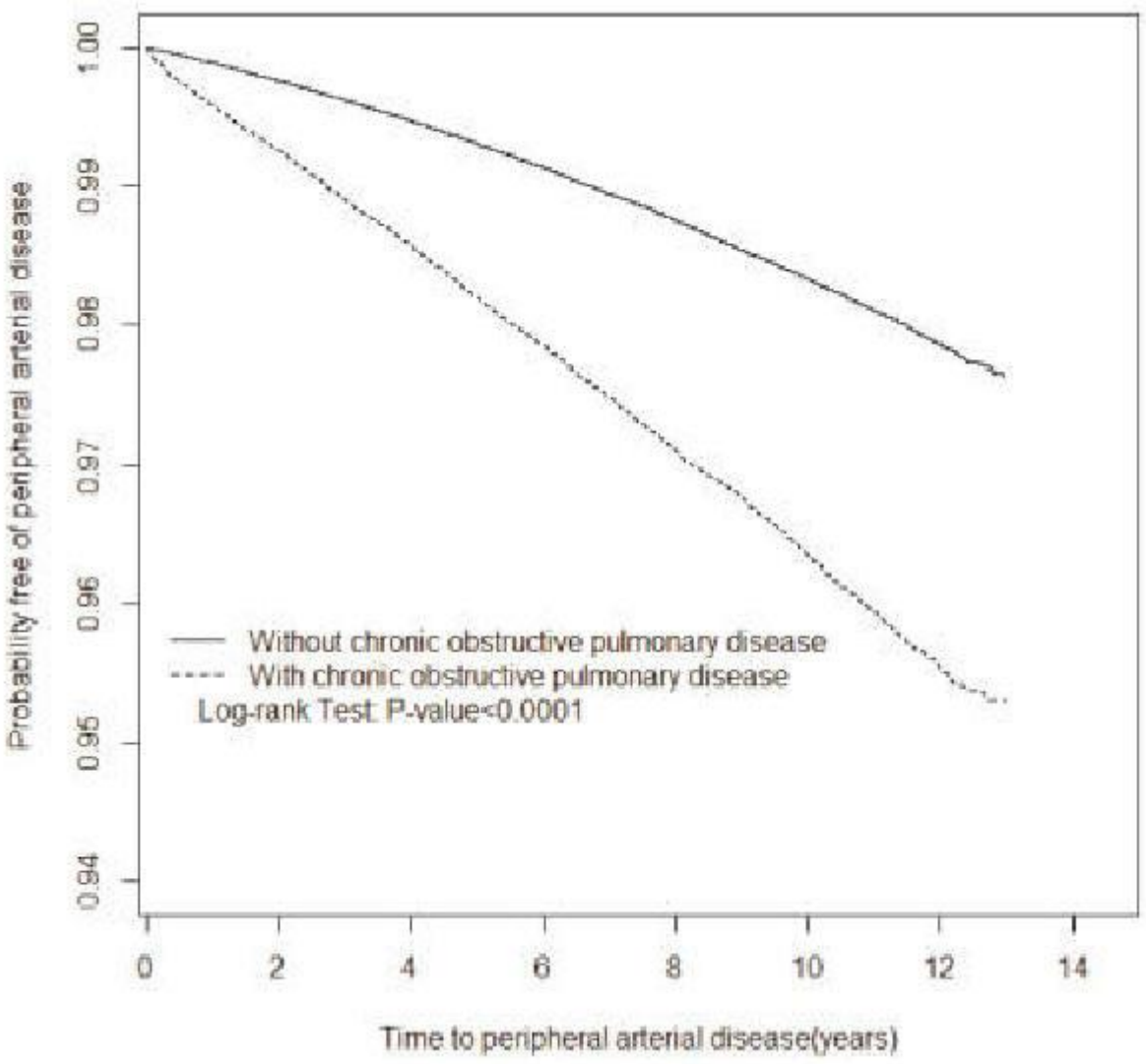
Figure. Probability free of PAD for patients with (dashed line) and without (solid line) COPD.



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INCREASE RISK OF ERECTILE DYSFUNCTION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS : A POPULATION-BASED COHORT STUDY.

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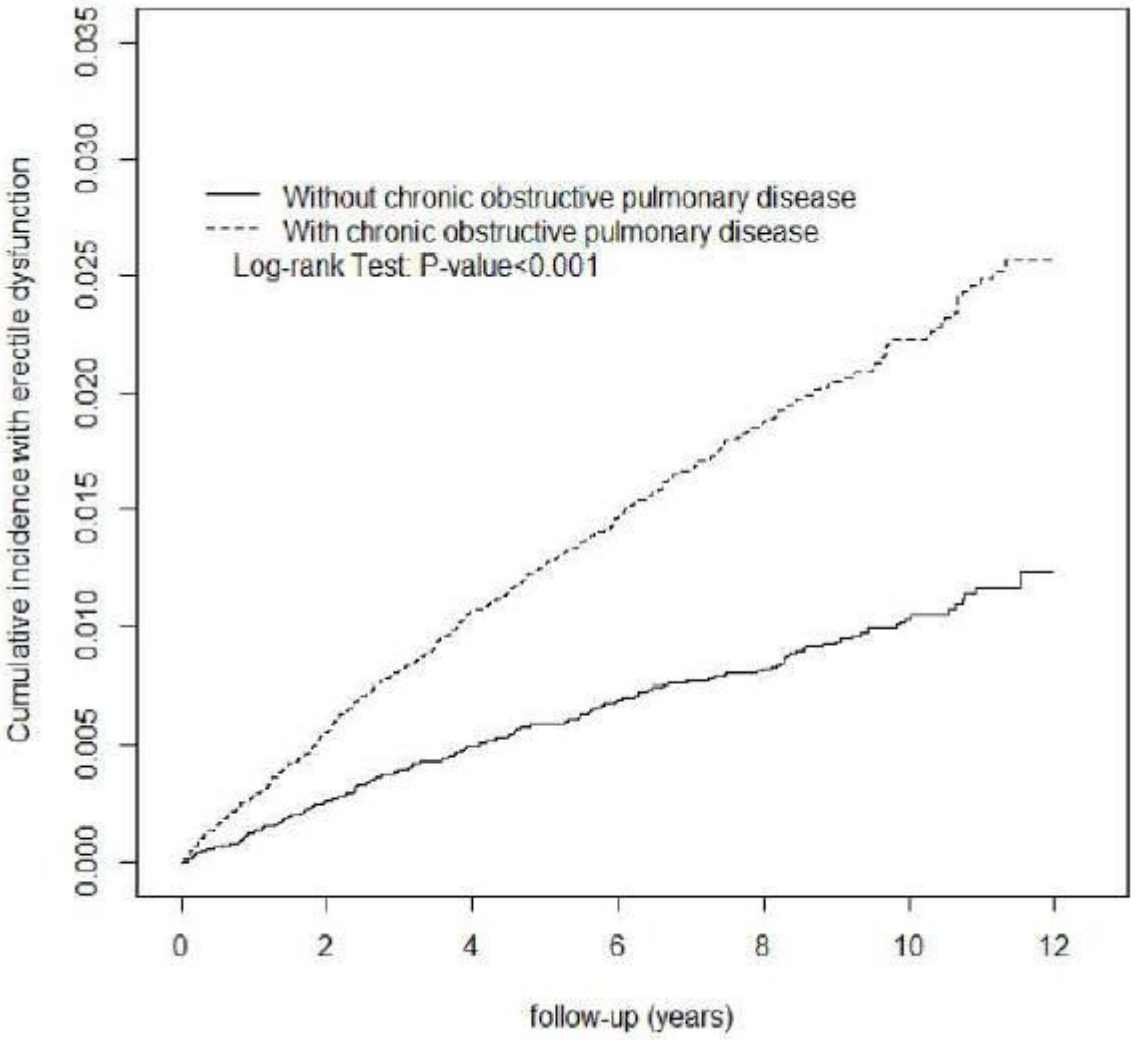
Background: The prevalence of sexual dysfunction in patients with chronic obstructive pulmonary disease (COPD) seemed high; however, large scale of population-basedstudy was absent. We examined the risk of erectile dysfunction (ED) among patients with COPD in a nationwide population-based study.

Methods: We conducted a retrospective cohort study using data from the National Health Insurance (NHI) system of Taiwan. The COPD cohort included 27,151 newly diagnosed males between 2000 and 2011. Each patient was randomly matched with another male person without COPD according to age and the index year. The occurrence of ED was followed up until the end of 2011. The relative risks of ED were estimated using the Cox proportional hazard model after adjusting for age, index year and comorbidities.

Results: The overall incidence of ED was 2.17-fold greater in the COPD cohort than in the non-COPD cohort [23.6 versus 10.8 per 10000 person-years; 95% confidence interval(CI) = 1.84–2.56]. Compared to non-COPD patients, the risk increased with thenumber of ER visits and admissions for COPD acute exacerbation from 1.87 (95% CI = 1.57–2.21) to 6.80 (95% CI = 3.78–12.2) and 1.86 (95% CI = 1.57–2.20) to 16.5(95% CI = 8.63–31.7).

Conclusions: Patients with COPD had a significantly higher risk of developing ED compared to the general population. The results also support that poor control of COPD status is a key factor affecting ED development.

Figure. Cummulative incidence of erectile dysfunction in patients with (dashed line) or without (solid line) chronic obstructive pulmonary disease.



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SMOKING CESSATION AS A REDUCING RISK OF DEVELOPPING CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Background: COPD is an irreversible lung disease that gradually and insidiously whose frequency increases with age. According to the World Health Organization,COPD could become the third leading cause of death worldwide by 2030. The main cause (in 80%) is the active and passive smoking. Other risk factors for COPD include air pollution and exposure to chemicals at workplace. At present, no treatment to this disease is curative.The only preventive measure that could slow the progression of the disease is smoking cessation. In the pneumology and pulmonary rehabilitation at Kabaya hospital in Rwanda, 71% of patients aged 40-75 years with COPD were former smokers.

Methods: The aim of this study was to compare two groups of patients and to evaluate the importance of smoking cessation in patients with COPD who are treated following 30 people, including 19 men and 11 women aged 40 to 68 for one year (July 2013-July 2014). Among them, 13 people continued to smoke after diagnosis and 17 others arrested tobacco. We used data included in their medical records and those we collected at each visit.

Results: Those who continued to smoke consulted 3 times more than those who stopped smoking (68% against 32%) for COPD exacerbations include chronic cough, shortness of breath and sputum. Out of 13 patients who continued to smoke, 9 have developed the most severe forms of the disease (69.3% against 30.7%)among those who stopped smoking).Note also depression among smokers (34%).

Conclusion: Smoking contributes to the degree of severity of COPD and its judgment should be prioritized for effective therapy. Although quitting smoking will not recover the patient's lung function at an advanced stage of the disease, it will improve its decline. The lifestyle is taken into account in the management, given the high incidence of depression.

Disclosure: No commercial funding is declared

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EXACERBATIONS AMONG COPD PATIENTS: 2ND REASON FOR CONSULTATION IN PNEUMOLOGY DEPARTMENT AT BUGESERA DISTRICT HOSPITAL (RWANDA)

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Background: Chronic obstructive pulmonary disease (COPD) affects many people in the world and most of them are unaware. Its evolution is marked by exacerbations episodes widely varying from a patient to another and may be triggered by infection, exposure and inhalation of fumes, dust, minerals among others. In 1/3 cases, no precipitating cause is identified. Most exacerbations can be treated in outpatient. The existence of gravity waves requires hospitalisation. Respiratory diseases were the second cause for consultation all ages confused in Rwanda health centers in 2013 or 22.5%. The mortality rate during hospitalization for COPD exacerbations is estimated between 2.5 and 10%.

Methods: The objective of our study was to identify the causes of exacerbations in COPD patients receiving treatment. We conducted our research in Pneumology department for 3 months from July 2014 to October 2014 by interviewing patients in acute phase of COPD or showing signs of clinical worsening. We interviewed 54 people, aged 45 to 76 years including 38 men and 16 women through predefined questionnaire. Fifteen-minute interview in the local language, Kinyarwanda, as this hospital is located in a rural area where the illiteracy rate is very high.

Results: Sixteen percent of patients have consulted for chronic cough, 21% for excessive sputum, 54% cough and sputum, 7.5% dyspnoea and 1.5% for fever. Among all patients, 69% were former smokers and 23% of current smokers, 6% were exposed to passive smoking and 2% former miners. Fifty one percent interrupted their initial therapy, 7% following another treatment and in 42% the cause is not known.

Conclusion: Smoking cessation and treatment adherence could be benefited to limit the frequency of exacerbations. The management should cover three areas: etiological, diagnostic and therapeutic.

Disclosure: No commercial funding is declared

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FREE TRIPLE COMBINATION OF GLYCOPYRRONIUM, INDACATEROL AND ICS IMPROVES LUNG FUNCTION AND DYSPNOEA VERSUS FREE DOUBLE COMBINATION OF INDACATEROL AND ICS IN PATIENTS WITH COPD: POST-HOC ANALYSIS FROM GLOW6 STUDY

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Background: The GLOW6 study earlier reported rapid onset and sustained bronchodilation with co administration of indacaterol and glycopyrronium compared to indacaterol alone in patients with Chronic Obstructive Pulmonary Disease.[1] In this post-hoc analysis, we compared the effect of free triple combination use of glycopyrronium+indacaterol+inhaled corticosteroid versus indacaterol+inhaled corticosteroid on lung function and dyspnoea in a sub-group of patients using inhaled corticosteroid during the study.

Methods: The 12-week, multicentre, double-blind, parallel group GLOW6 study randomised 449 symptomatic patients with moderate to severe Chronic Obstructive Pulmonary Disease to glycopyrronium+indacaterol or indacaterol alone. 132 (29.4%) patients had ≥1exacerbations in the year prior to randomisation. 280 (62.6%) patients were on stable dose of inhaled corticosteroid at baseline and were allowed to continue inhaled corticosteroid during the study. We analysed this subgroup comparing free combination glycopyrronium+indacaterol+inhaled corticosteroid versus indacaterol+inhaled corticosteroid for improvements in trough FEV_1, FEV_1 area under the curve from 0 to 4h ($AUC_{0\text{-}4h}$), and transition dyspnoea index.

Results: Of the 280 patients, 138 were on glycopyrronium+indacaterol+inhaled corticosteroid and 142 on indacaterol+inhaled corticosteroid. Compared to free combination of indacaterol+inhaled corticosteroid, free combination of glycopyrronium+indacaterol+inhaled corticosteroid significantly improved trough FEV_1 (mean treatment difference [MTD] 64mL; p=0.021) at week 12, FEV_1 $AUC_{0\ 4h}$ on Day1 (MTD 111mL; p<0.001) and at week 12 (MTD 118 mL; p<0.001) and dyspnoea in terms of transition dyspnoea index score (MTD 0.7; p=0.041). The overall safety was comparable between glycopyrronium+indacaterol+inhaled corticosteroid and indacaterol+inhaled corticosteroid groups.

Conclusion: Over 12 weeks, the free triple combination (glycopyrronium+indacaterol+inhaled corticosteroid) showed significantly better improvements in lung function and dyspnoea compared to the free double combination (indacaterol+inhaled corticosteroid) in symptomatic patients with moderate-to-severe Chronic Obstructive Pulmonary Disease and was comparable in safety.

Reference :

1. Vincken W, et al. Int J Chron Obstruct Pulmon Dis. 2014; 9: 215–228

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THE "FREQUENT EGZACERBATOR" PHENOTYPE: ENDOTHELIAL DYSFUNCTION AND SYSTEMIC INFLAMMATION

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Background: Endothelial dysfunction is a possible link between increased cardiovascular mortality and systemic inflammation in patients with COPD. Previous studies suggest an association between acute exacerbation of COPD and deterioration of endothelial function, but so far systematic studies of endothelial dysfunction in two phenotypically distinct groups of COPD patients has not been done.

Aim: The aim of this study was to investigate whether there are differences in endothelial function and systemic inflammation between the two groups of COPD patients: „frequent exacerbator" and „infrequent exacerbator".

Methods: 117 patients were enrolled. COPD patients were divided into two groups according to the criteria of frequency of acute exacerbation: 41 frequent exacerbator and 41 infrequent exacerbator. The control group consists of 35 healthy smokers. In all three groups were determined vWF as a marker of endothelial dysfunction and CRP and fibrinogen as markers of systemic inflammation.

Results: We found an increase of all markers of endothelial function and sistemic inflammation in the frequent exacerbator group compared to the infrequent exacerbator group and compared to the healthy control group. The differences found were statistically significant in all cases ($p<0,001$).

Conclusion: Between the two phenotypic groups of COPD patients, there is a difference in the degree of endothelial dysfunction and systemic inflammation.

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THE ROLE OF SURFACTANT PROTEIN D IN CIGARETTE SMOKE-INDUCED PULMONARY PATHOLOGY

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Background: Surfactant protein D (SP-D) is a calcium-dependent carbohydrate molecule mainly produced by Type II pneumocytes and Clara cells in the lung. SP-D is involved in the innate immune system acting as an opsonin on the mucosal surfaces facilitating clearance of bacterial, viral, fungal or allergen challenge or other particulate material. SP-D deficient mice (*Sftpd-/-*) spontaneously develop pulmonary emphysema–like pathology accompanied by an increased number of apoptotic alveolar macrophages, phospholipid accumulation and oxidative stress markers. Cigarette smoke (CS) is the main cause for emphysema development in chronic obstructive pulmonary disease (COPD).

Hypothesis: We hypothesize that genetic ablation of SP-D leads to increased lung inflammation and that SP-D therapy may reduce inflammatory processes.

Methods: C57BL/6N *Sftpd+/+* and *Sftpd-/-* littermate male mice where exposed to CS for 2x50 min/5 days/12 weeks (chronic model) and control mice received room air. Administration of recombinant SP-D (rSP-D) (15ug) was given by intranasal inhalation one hour before CS exposure for 3 days (acute model).

Results: In the chronic smoke model the total cell count and ceramide content in bronchoalveolar lavage fluid (BALF) was significantly induced in CS exposed *Sftpd-/-* mice relative to *Sftpd+/+*mice. Corresponding SP-D dependent increase was seen for matrix metalloproteinase-12 gene expression. rSP-D therapy demonstrated a significant decrease in total cell infiltration in BALF after CS in both *Sftpd-/-* and *Sftpd+/+*mice.

Conclusion: The data indicate that SP-D has a dampening effect on CS induced pulmonary inflammation and SP-D based therapy has the potential to alleviate the cigarette smoked lung damage in COPD patients. The perspective of the study will now be to investigate how SP-D affects macrophage phagocytosis of particles from cigarette smoke.

Conflict of Interest: None

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THE DISTRIBUTION OF PHENOTYPES IN A POPULATION OF SEVERE COPD

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Background: COPD is a heterogeneous syndrome. Detailed information on the incidence of COPD phenotypes in the population is currently unavailable.

Aim: The analysis of the COPD population with severe bronchial obstruction in relation to clinically apparent phenotypes.

Methods: Non-interventional observational prospective Czech Multicentre Research Database of COPD focusing on the collection and data analysis of COPD population with post-BD FEV_1< 60%. More at ClinicalTrials.gov, NCT01923051.

Results: In the first six months we enrolled 190 consecutive patients (67,0 years, 77,4% males, 8,4% non-smokers) with post-BD FEV_1 42%. All categories were included (A 5,8%, B 20%, C 11%, D 63,2%). Clinically apparent phenotypes were present in all patients (more than one phenotype in 44,2% subjects). In addition to the bronchitic and emphysematic phenotypes, the database identified frequent exacerbators in 23,2%, asthma+COPD overlap in 11,1%, bronchiectasis+COPD overlap in 2,1% and pulmonary cachexia in 8,9% of severe COPD subjects. Some phenotypes were significantly associated with the presence of particular comorbidities (more cardiac comorbidities and upper airway impairment in the bronchitic phenotype, more osteoporosis in the emphysematous phenotype) and clinical parameters (lower KCO and higher oxygen desaturation during 6-minute walking test in emphysematous phenotype). Mucus predominance in CAT was significantly associated with bronchitic phenotype.

Conclusion: Preliminary analysis of baseline data demonstrates the variability of clinical parameters in patients with severe COPD. The effectiveness of a phenotype oriented approach to patients with COPD will be assessed by prospective follow-up of our patients.

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EXPRESSION OF MATRIX METALLOPROTEINASES IN BRONCHOALVEOLAR CELLS IN COPD AND IN COPD PHENOTYPES

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Introduction: Matrix metalloproteinases (MMP) are a group of proteases involved in the pathogenesis of COPD. However, there is limited information about their expression profiles in bronchoalveolar cells from patients with different phenotypes of COPD.

Objectives: To assess expression of mRNA for certain MMPs and their inhibitors (TIMP) in bronchoalveolar cells in COPD and to compare the expression of mRNA for MMPs and TIMP in COPD and controls and between certain phenotypes of COPD.

Methods: A total of 31 COPD patients and 33 controls were included in the study. All subjects underwent flexible bronchoscopy and bronchoalveolar lavage, cytological examination of the bronchoalveolar fluid (BALF) and determination of relative expression of mRNA for MMP-2, MMP-9 and TIMP-1 in bronchoalveolar cells. In the subsequent two years, all COPD patients were followed for frequency of exacerbations and symptoms. Then the COPD patients were divided into subgroups according their phenotypes: frequent exacerbators (≥2 exacerbations per year) and non-frequent exacerbators; and with or without chronic bronchitis.

Results: The group of COPD patients comprised 16 patients with bronchitic phenotype, 15 patients without bronchitic phenotype, 11 frequent exacerbators and 20 non-frequent exacerbators. The COPD patients had higher expression of mRNA for MMP-9 (0.036 vs.0.017, p=0.026), MMP-2 (0.043 vs. 0.021, p=0.016) and TIMP-1 (2.30 vs. 0.82, p=0.014) than control group. The COPD patients with bronchitic phenotype had lower expression of mRNA for MMP-9 (0.000 vs. 0.082, p=0,038), MMP-2 (0.015 vs. 0.068, p=0,149) and higher expression of mRNA for TIMP-1 (3.24 vs. 2.16, p=0,120) than patients without bronchitic phenotype, however difference of expression of mRNA for MMP-2 and TIMP-1 between both groups did not achieve statistical significance. Frequent exacerbators had lower expression of mRNA for MMP-9 (0.008 vs.0.069, p=0.012), MMP-2 (0.011 vs. 0.051, p=0.086) and TIMP-1 (0.97 vs. 2.36, p=0.048) than non-frequent exacerbators.

Conclusions: Expression of mRNA for MMP-9, MMP-2 and TIMP-1 is elevated in COPD and different in various COPD phenotypes.