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Simvastatin for the prevention of exacerbations in moderate-to severe COPD

Authors: Criner GJ, et al.

Reference: N Engl J Med 2014; 370: 2201-10.

URL: <http://www.nejm.org/doi/full/10.1056/NEJMoa1403086>

Comment: Statins have been reported to have anti-inflammatory effects, and several retrospective studies have shown that statins are beneficial in COPD in terms of reductions in rates of hospitalization, lung function decline, and mortality. However, there has been no large-scale prospective study on the efficacy of statins in patients with COPD. The investigators designed the Prospective Randomized Placebo-Controlled Trial of Simvastatin in the Prevention of COPD Exacerbations (STATSCOPE) as a randomized, controlled trial of simvastatin (40 mg per day) vs. placebo, with annual exacerbation rates as the primary outcome. They enrolled moderate-to-severe patients with COPD (FEV1 %predicted <80%, pack-years ≥ 10) who were receiving supplemental oxygen or treatment with glucocorticoids or antibiotics, or had had an emergency department visit or hospitalization for COPD within the past year. Participants were treated from 12 to 36 months at 45 centers. A total of 885 patients with COPD were enrolled (simvastatin, N=433; placebo, N=452).

As a result, the mean number of exacerbations per person-year was similar in the simvastatin and placebo groups (1.36 ± 1.61 vs. 1.39 ± 1.73 , $p=0.54$). The median number of days to the first exacerbation was also similar (223 day vs. 231 days, $p=0.34$). Furthermore, simvastatin had no effect on lung function, quality of life, the rate of severe adverse events, or mortality.

This study only enrolled moderate-to-severe patients with COPD, and it is unclear whether simvastatin would not be beneficial to patients with milder airflow limitation. Nevertheless, the results of this study may be disappointing to many respiratory physicians who have favorably looked at several previous studies on statins. We, however, have to realize that such a well-planned, randomized, and placebo-controlled study would be necessary in order to finally confirm a hypothesis generated from any retrospective and/or observational studies.

Tiotropium respimat inhaler and the risk of death in COPD

Authors: Wise RA, et al.

Reference: N Engl J Med 2013; 369: 1491-501.

URL: <http://www.nejm.org/doi/full/10.1056/NEJMoa1303342>

Comment: Tiotropium, a long-acting inhaled anticholinergic bronchodilator, is marketed as a dry-powder formulation delivered by means of the HandiHaler inhalation device (at a dose of 18 μg) and as an aqueous solution delivered by means of the Respimat inhaler (at a dose of 5 μg), and crossover trials of the both devices have shown similar efficacy and pharmacokinetic profiles. On the other hand, there has been concern about the safety of tiotropium because more deaths were reported with tiotropium Respimat than with placebo in a post hoc pooled analysis of placebo-controlled trial and subsequent meta-analyses and reviews of the Respimat trials

database. Then, the investigators designed the tiotropium Safety and Performance in Respimat (TIOSPIR) trial as a randomized, prospective evaluation of the safety and efficacy of tiotropium Respimat, as compared with tiotropium HandiHaler. A total of 17,135 patients with COPD received at least one dose of the assigned treatment (Respimat 2.5 µg, 5 µg, or HandiHaler 18 µg per day). Primary end points were the risk of death (noninferiority study for both doses of Respimat vs. HandiHaler) and the risk of the first COPD exacerbation (superiority study for Respimat 5 µg vs. HandiHaler). Cardiovascular safety was also assessed.

During a mean follow-up of 2.3 years, Respimat was noninferior to HandiHaler with respect to the risk of death and not superior to HandiHaler with respect to the risk of the first exacerbation. Causes of death and incidences of major cardiovascular adverse events were similar in the three groups.

These results address a caution when interpreting safety outcomes from meta-analyses of small data sets and observational studies. The authors insist that post hoc meta-analyses without an a priori hypothesis should be considered hypothesis-generating rather than definitive, and that observational studies may be flawed because of residual confounding factors that are presumably balanced in a randomized clinical trial. However, it must be noted that this study did not have a placebo group; therefore, it cannot be concluded from this study that tiotropium Respimat reduces mortality in patients with COPD.

Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study

Authors: Ekström MP, et al.

Reference: BMJ 2014; 348: g445.

URL: <http://www.bmj.com/content/348/bmj.g445.long>

Comment: COPD is a major cause of breathlessness and benzodiazepines and opioids may be able to relieve chronic refractory breathlessness. However, safety data for benzodiazepines and opioids in patients with severe COPD are limited. The investigators designed a population based longitudinal consecutive cohort study of patients starting long-term oxygen therapy for COPD in Sweden between 2005 and 2009. A total of 2249 patients were analyzed and benzodiazepines were used by 535 (24%) patients and opioids by 509 (23%), and 200 (9%) were taking both types of drug at baseline. Benzodiazepines and opioids were not associated with increased admission (hazard ratio (HR) 0.98 and 0.98, respectively). On the other hand, benzodiazepines were associated with increased mortality (HR 1.21) with a dose response trend. Opioids also had a dose response relation with mortality; however, lower dose opioids (≤ 30 mg oral morphine equivalents per day) were not associated with increased mortality (HR 1.03) in contrast with higher dose opioids (HR 1.21). Concurrent benzodiazepines and opioids in lower doses were not associated with increased admissions or mortality.

This study seems to be very important because the findings support the safety of regular low dose systemic opioids to reduce breathlessness in severe COPD patients. The investigators suggest that benzodiazepines should not be the first line treatment for breathlessness. Instead, sustained release morphine should be considered as a first line treatment and should be initiated at a low dose.

Effect of β blockers on mortality after myocardial infarction in adults with COPD: population based cohort study of UK electronic healthcare records

Authors: Quint JK, et al.

Reference: BMJ 2013; 347: f6650.

URL: <http://www.bmj.com/content/347/bmj.f6650>

Comment: Patients with COPD are at increased risk of cardiovascular comorbidities including myocardial infarction. β blockers are effective at reducing risk of mortality and re-infarction after myocardial infarction. Despite accumulating evidence that β blockers are safe and beneficial in patients with COPD but their use continues to be limited because of historical concern that β blockers are harmful in patients with COPD by potentially inducing bronchospasm. The investigators designed a population based cohort study using UK national registry of myocardial infarction (Myocardial Ischaemia National Audit Project (MINAP)) linked to the General Practice Research Database (GPRD), 2003-11. Among 1063 patients with COPD with a first myocardial infarction, treatment with β blockers started during the hospital admission was associated with substantial survival benefits during a median follow-up of 2.9 years (HR 0.50). Patients already taking a β blocker before their myocardial infarction also had a survival benefit (HR 0.59).

These results support that β blockers should be used more widely in patients with COPD who have had myocardial infarction. Interestingly, the decrease in mortality was due to a reduction of both cardiac and non-cardiac deaths. It has been suggested that the benefit of β blockers may come from non-cardiac effects, which may, in turn, explain the reduction in the non-cardiac deaths of this study.

Minimum clinically important difference for the COPD Assessment Test: a prospective analysis

Authors: Kon SS, et al.

Reference: Lancet Respir Med 2014; 2: 195-203.

URL: [http://www.thelancet.com/journals/lanres/article/PIIS2213-2600\(14\)70001-3/abstract](http://www.thelancet.com/journals/lanres/article/PIIS2213-2600(14)70001-3/abstract)

Comment: The COPD Assessment Test (CAT) is a simple, eight item, health status instrument for patients with COPD, and has been incorporated into the GOLD combined assessment of COPD. However, the minimum clinically important difference (MCID) has not been established. The investigators aimed to estimate the MCID for the CAT in three different clinical settings: response to 8 weeks of outpatient pulmonary rehabilitation (study 1; 565 patients had paired CAT scores), recovery after admission to hospital (from hospital discharge to 3 months after discharge) for acute exacerbation of COPD (study 2; 147 patients had paired CAT scores), and longitudinal change (at baseline and at 12 months) in stable outpatients with COPD (study 3; 164 patients had paired CAT scores). In all of the studies, the change in CAT score was significantly correlated with the change in SGRQ score. Linear regression estimated the minimum clinically important improvement for the CAT to range between -1.2 and -2.8 with receiver oper-

ating characteristic curves consistently identifying -2 as the MCID. Taken together, the most reliable estimate of the MCID of the CAT is 2 points. Because the CAT score is extensively being used and will be so further worldwide, this information would be highly useful in the assessment and interpretation of CAT data in daily practice and/or in any future interventional clinical studies.

Twice daily N-acetylcysteine 600 mg for exacerbations of chronic obstructive pulmonary disease (PANTHEON): a randomised, double-blind placebo-controlled trial

Authors: Zheng JP, et al.

Reference: Lancet Respir Med 2014; 2: 187-94.

URL: [http://www.thelancet.com/journals/lanres/article/PIIS2213-2600\(13\)70286-8/abstract](http://www.thelancet.com/journals/lanres/article/PIIS2213-2600(13)70286-8/abstract)

Comment: N-acetylcysteine is an effective mucolytic drug that has antioxidant properties. Although N-acetylcysteine has been reported to significantly reduce the risk of COPD exacerbations, inconsistent results have also been reported. The investigators hypothesized that high-dose (1200 mg per day) and long-term (1 year) N-acetylcysteine treatment could reduce the rate of exacerbations in COPD, and designed the Placebo-controlled study on efficacy and safety of N-acetylcysteine High dose in Exacerbations of chronic Obstructive pulmonary disease (PANTHEON) study as a prospective, randomized, double-blind, placebo-controlled, parallel-group study. A total of 1006 Chinese patients with moderate-to-severe COPD (FEV1 of 30-70% of predicted) were enrolled (N-acetylcysteine, N=504; placebo, N=502). The primary endpoint was exacerbation rate in 1 year. As a result, treatment of twice daily N-acetylcysteine 600 mg was associated with a reduction in COPD exacerbations compared with placebo (1.16 vs. 1.49 exacerbations per patient-year, risk ratio 0.78, p=0.0011). Time to first exacerbation did not differ between treatment groups, but time to second and third exacerbation was shorter in the placebo group than the N-acetylcysteine group. They noted no interaction between treatment effect and inhaled corticosteroid use, suggesting the treatment effect was independent of inhaled corticosteroid use.

This study suggests that high-dose N-acetylcysteine treatment may be effective for the reduction in COPD exacerbations. However, this study was performed only in Chinese patients with moderate-to-severe COPD patients, and did not analyze the treatment effect based on COPD phenotypes (e.g. emphysema severity or presence of chronic bronchitis). Therefore, further investigations would be warranted in order to clarify what kind of patients with COPD would benefit more with N-acetylcysteine treatment.



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Once-daily indacaterol versus tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE): a randomised, blinded, parallel-group study

Authors: Decramer ML, et al.

Reference: Lancet Respir Med 2013; 1: 524-33.

URL: [http://www.thelancet.com/journals/lanres/article/PIIS2213-2600\(13\)70158-9/abstract](http://www.thelancet.com/journals/lanres/article/PIIS2213-2600(13)70158-9/abstract)

Comment: Long-acting β_2 agonists (LABA; e.g. indacaterol) and long-acting muscarinic antagonists (LAMA; e.g. tiotropium) have been used for treatment of stable patients with COPD. On the other hand, prevention of COPD exacerbations is a key treatment goal of COPD disease management. The investigators designed the indacaterol: providing opportunity to reengage patients with life (INVIGORATE) study as a 52 week, international, multi-center, randomised, blinded, double-dummy, parallel group study comparing the effects of once-daily indacaterol maleate (150 μg) and tiotropium bromide (18 μg). Primary and key secondary objectives were to investigate whether indacaterol was non-inferior to tiotropium for trough FEV₁ at week 12 (primary endpoint), and for rate of exacerbations at week 52 (secondary endpoint). A total of 3444 patients with moderate-to-severe COPD (FEV₁ of 30-50% of predicted) and a history of at least one moderate to severe exacerbation in the previous 12 months were enrolled (indacaterol, N=1723; tiotropium, N=1721). At week 12, indacaterol was non-inferior to tiotropium for trough FEV₁. However, Indacaterol did not show non-inferiority in terms of annualized exacerbation rates: 0.79 (indacaterol) vs. 0.61 (tiotropium). There was no difference in the number of patients who had adverse events between the two groups.

In this study, indacaterol was non-inferior to tiotropium in terms of lung function with comparable safety profiles but failed to show non-inferiority in terms of exacerbation rates. The investigators insist that the absolute number of exacerbation events was small and the difference between treatments is of uncertain clinical importance. This opinion may be true because the dual bronchodilator (LABA/LAMA) has been available and indacaterol/glycopyrronium was superior in preventing moderate-to-severe COPD exacerbations compared with glycopyrronium alone or open-label tiotropium in the SPARK study. Further clinical trials would be needed in order to determine how LABA, LAMA, inhaled corticosteroids, and their combinations should be used for the prevention of COPD exacerbations.

New Impact factor and ranking for Respiriology released July 2014



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Risk factors and comorbidities in the preclinical stages of chronic obstructive pulmonary disease

Authors: Van Remoortel H, et al.

Reference: Am J Respir Crit Care Med 2014; 189: 30-8.

URL: <http://www.atsjournals.org/doi/abs/10.1164/rccm.201307-1240OC>

Comment: Comorbidities are important factors for health status and mortality in patients with COPD. However, most studies addressing comorbidities in COPD have been conducted in symptomatic patients especially with moderate-to-severe COPD and there is little information about comorbidities and their risk factors in the preclinical stages of COPD. The investigators compared 60 subjects with preclinical COPD (FEV1/FVC $61 \pm 7\%$, FEV1 %predicted $87 \pm 29\%$) to 60 smoking control subjects and 60 never-smoking control subjects participating in a lung cancer screening trial (NELSON). The prevalence of premorbid risk factors and comorbid diseases was significantly higher in preclinical COPD compared with never-smoking control subjects, but was similar to smoking control subjects. In preclinical COPD and smoking control subjects, the combination of cardiovascular disease and musculoskeletal disease was the most prevalent. A multivariate logistic regression analysis showed that physical inactivity and smoking, but not airflow limitation, were independent risk factors for having greater than or equal to two comorbidities. Importantly, no statistical interaction was found between preclinical COPD and other risk factors (aging, obesity, systemic inflammation, and physical inactivity) indicating that there was no potentiation of risk by the presence of COPD.

These findings suggest that COPD is one concomitant disease in a multimorbid condition in response to common risk factors, and challenge the current concept that COPD is an independent risk factor for metabolic, musculoskeletal, and cardiovascular disease. Smoking and physical inactivity might be appropriate targets for prevention of multimorbidity in the elderly people.

Outgrowth of the bacterial airway microbiome after rhinovirus exacerbation of chronic obstructive pulmonary disease

Authors: Molyneaux PL, et al.

Reference: Am J Respir Crit Care Med 2013; 188: 1224-31.

URL: <http://www.atsjournals.org/doi/abs/10.1164/rccm.201302-0341OC>

Comment: The majority of COPD exacerbations are caused by respiratory infections with bacteria and/or viruses, and it was reported that rhinovirus infection is followed by significantly increased frequencies of positive sputum cultures in COPD. However, it remains unclear whether these represent de novo infections or an increased load of organisms from the complex microbial communities (microbiome) in the lower airways. The investigators investigated the effect of rhinovirus infection on the airway bacterial microbiome with subjects with mild COPD (GOLD 2, n=14) and healthy control subjects (n=17). The subjects were inoculated intranasally with low-dose rhinovirus-16 using an atomizer. Induced sputum was collected at baseline and days 5, 12, and 42, and DNA was extracted. At 15 days after rhinovirus infection, there was a six-fold

increase in 16S rRNA gene copy number and a 16% rise in numbers of proteobacterial sequences, most notably in potentially pathogenic *Haemophilus influenzae*, from a preexisting community. These changes occurred only in the sputum microbiome of subjects with COPD and were still evident 42 days after infection in contrast with the temporal stability demonstrated in the microbiome of healthy control subjects.

This study showed for the first time that rhinovirus infection could affect the microbiome in the lung, and suggests that outgrowth from an existing bacterial community rather than acquisition of new bacterial species contributes to the increased bacterial burden after rhinovirus infection in COPD patients. Further investigations will be warranted regarding the precise mechanism of the bacterial outgrowth. In addition, we are eager to learn what would actually happen in case of more severe disease with naturally occurring viral exacerbations.

Clinical features and determinants of COPD exacerbation in the Hokkaido COPD cohort study

Authors: Suzuki M, et al.

Reference: Eur Respir J 2014; 43:1289-97.

URL: <http://erj.ersjournals.com/content/43/5/1289.long>

Comment: Exacerbations are among the major factors that may affect the natural history of COPD. The Hokkaido COPD cohort study is a carefully designed, multi-center, observational cohort study conducted in Japan. A unique finding of this cohort study was that the exacerbation frequency was much lower than the previous large-scale clinical trials. However, the characteristics and risk of exacerbations in a population with such low exacerbation frequency have not yet been clarified. The investigators examined the clinical characteristics and determinant of COPD exacerbations using a total of 268 subjects who had clinical data for multiple visits. Exacerbation was defined in multiple ways: patient's subjective complaint, symptom definition, requiring prescription change, requiring antibiotic treatment, and requiring hospital admission. Exacerbation frequency (events/person/year) was 0.78 ± 1.16 (subjective complaint), 0.24 ± 0.47 (symptom definition), 0.20 ± 0.43 (prescription definition), 0.13 ± 0.28 (antibiotic definition), and 0.06 ± 0.19 (admission definition). Exacerbation events did not significantly affect the annual decline in FEV1. A high St. George's Respiratory Questionnaire total score, especially its Activity score, and a low body mass index were strongly associated with exacerbation-free survival, exacerbation frequency, and development of recurrent exacerbations.

National characteristics such as the health care system and socioeconomic status may affect the low frequency of exacerbations in Japan nowadays compared to the other geographical regions on the globe, because we used to see far more patients with COPD who were hospitalized with exacerbation some decades ago. Nevertheless, these results suggest that it would be highly important to identify patients at risk for exacerbation who have limited physical activities and/or weight loss. We have to make every effort to reduce the risk of exacerbation by optimal pharmacotherapy, rehabilitation, and nutritional support even in a population with low exacerbation frequency.

**Thank you to those who attended the 19th APSR conference!
We hope to see you all next year at the 20th APSR conference
in Kuala Lumpur, Malaysia!**



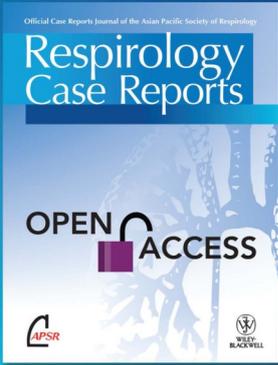
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