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Articles selected and commented on by: Chin Kook Rhee

Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Seoul St Mary’s Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

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Association of Cardiovascular Risk With Inhaled Long-Acting Bronchodilators in Patients With Chronic Obstructive Pulmonary Disease: A Nested Case-Control Study

Authors: Wang MT et al.
URL: https://www.ncbi.nlm.nih.gov/pubmed/29297057

Comments:
The authors aimed to investigate risk of CVD associated with LABAs and LAMAs, focusing on the initiation and duration of LABA and LAMA therapies. This nested case-control study included 284,220 LABA-LAMA-naïve patients, retrieved from the Taiwan National Health Insurance Research Database for health care claims from 2007 to 2011. Cases with inpatient or emergency care visits for coronary artery disease, heart failure, ischemic stroke, or arrhythmia were identified and individually matched to 4 randomly selected controls. During a mean follow-up of 2.0 years, 37,719 patients with CVD (mean age, 75.6 years; 71.6% men) and 146,139 matched controls (mean age, 75.2 years; 70.1% men) were identified. New LABA and LAMA use in COPD was associated with a 1.50-fold (95% CI, 1.35-1.67; P < 0.001) and a 1.52-fold (95% CI, 1.28-1.80; P < 0.001) increased cardiovascular risk within 30 days of initiation, respectively, whereas the risk was absent, or even reduced with prevalent use. LABA/LAMA has been known to be safe, however, this study raised the issue of safety of this drug. Although this study is retrospective, large number of patients were analyzed. Further prospective study regarding safety of LABA/LAMA is needed.

Total Airway Count on Computed Tomography and the Risk of Chronic Obstructive Pulmonary Disease Progression. Findings from a Population-based Study

Authors: Kirby M et al.
URL: https://www.ncbi.nlm.nih.gov/pubmed/28886252

Comments:
Studies of excised lungs show that significant airway attrition in the "quiet" zone occurs early in COPD. The authors aimed to determine if the total number of airways quantified in vivo using CT reflects early airway-related disease changes and is associated with lung function decline independent of emphysema in COPD. Participants in CanCOLD (Canadian Chronic Obstructive Lung Disease) study underwent inspiratory/expiratory CT at visit 1; spirometry was performed at four visits over 6 years. CT total airway count (TAC) was measured as
well as airway inner diameter and wall area using anatomically equivalent airways. Participants included never-smokers (n = 286), smokers with normal spirometry at risk for COPD (n = 298), GOLD I COPD (n = 361), and GOLD II COPD (n = 239). TAC was significantly reduced by 19% in both GOLD I and GOLD II compared with never-smokers (P < 0.0001) and by 17% in both GOLD I and GOLD II compared with at-risk participants (P < 0.0001) after adjusting for low-attenuation areas. Further analysis revealed parent airways with missing daughter branches had reduced inner diameters (P < 0.0001) and thinner walls (P < 0.0001) compared with those without missing daughter branches. Among all CT measures, TAC had the greatest influence on FEV1 (P < 0.0001), FEV1/FVC (P < 0.0001), and bronchodilator responsiveness (P < 0.0001). TAC was independently associated with lung function decline (FEV1, P = 0.02; FEV1/FVC, P = 0.01). TAC may reflect the airway-related disease changes that accumulate in the "quiet" zone in early/mild COPD. Little study has shown the importance of TAC in COPD. Early COPD is very important, however, little biomarker has been existed. TAC may be a biomarker to predict accelerated COPD progression.

**Long-term Use of Inhaled Corticosteroids in COPD and the Risk of Fracture**

**Authors:** Gonzalez AV et al.


**URL:** https://www.ncbi.nlm.nih.gov/pubmed/28716642

**Comments:**

It is uncertain whether long-term use of ICS increases the risk of fracture, particularly in women, in view of the postmenopausal risks. The authors assessed whether long-term ICS use in patients with COPD increases the risk of hip or upper extremity fractures, and examined sex-related differences. The Quebec health-care databases were used to form a cohort of patients with COPD over 1990 to 2005, followed until 2007 for the first hip or upper extremity fracture. In a nested case-control analysis, each case of fracture was matched with 20 control subjects on age, sex, and follow-up time. The adjusted rate ratio (RR) of fracture with ICS use, by duration and dose, was estimated using conditional logistic regression, with an interaction term to compare the risk in men and women. In the cohort of 240,110 subjects, 19,396 sustained a fracture during a mean 5.3 years (rate, 15.2 per 1,000 per year). Any use of ICSs was not associated with an increased rate of fracture (RR, 1.00; 95% CI, 0.97-1.03). The fracture rate was increased with > 4 years of ICS use at daily doses ≥ 1,000 μg in fluticasone equivalents (RR, 1.10; 95% CI, 1.02-1.19). This risk increase did not differ between men and women. Long-term ICS use at high doses is associated with a modest increase in the risk of hip and upper extremity fractures in patients with COPD. This
dose-duration risk increase does not appear to be higher for women. This study analyzed large number of patients and the result is very informative. The adverse effect if ICS in COPD is very important issue. This study can provide good evidence for the risk of fracture by ICS. Physicians should be aware of potential risk of facture especially patients with long-term ICS use at high dose.

Fluticasone Furoate, Vilanterol, and Lung Function Decline in Patients with Moderate Chronic Obstructive Pulmonary Disease and Heightened Cardiovascular Risk

Authors: Calverley PMA et al.


URL: https://www.ncbi.nlm.nih.gov/pubmed/28737971

Comments:

Many patients COPD have an accelerated loss of lung function. It is unclear whether drug treatment can modify this in patients with moderately severe disease. In a prespecified analysis of the key secondary outcome in SUMMIT (Study to Understand Mortality and Morbidity), the authors investigated whether fluticasone furoate (FF; 100 μg), vilanterol (VI; 25 μg), or their combination (FF/VI) modified the rate of decline in FEV1 compared with placebo. The authors also investigated how baseline covariates affected this decline. Spirometry was measured every 12 weeks in this event-driven, randomized, placebo-controlled trial of 16,485 patients with moderate COPD and heightened cardiovascular risk. An average of seven spirometric assessments per subject among the 15,457 patients with at least one on-treatment measurement were used in the analysis of rate of FEV1 decline. The adjusted rates of FEV1 decline were -46 ml/yr (-3.0% of baseline) with placebo, -47 ml/yr (-3.1%) with VI, -38 ml/yr (-2.5%) with FF, and -38 ml/yr (-2.3%) with FF/VI. FF-containing regimens had lower rates of decline than placebo (P < 0.03), and FF/VI had a lower rate of decline than VI alone (P < 0.005). The FEV1 decline was faster in current smokers, those with a lower body mass index, males, and patients with established cardiovascular disease. In patients with moderate COPD and heightened cardiovascular risk, FF alone or in combination with VI appears to reduce the rate of FEV1 decline. To slow decline of FEV1 in COPD patients is one of the most important gold when managing COPD patients. The result of this study is quite compatible with previous post-hoc analysis of TORCH study (Am J Respir Crit Care Med 2008; 178: 332-338.). It should be further evaluated whether ICS/LABA can slow disease progression in COPD patients. Also, whether this effect is class one (whether other ICS also can slow FEV1 decline) should be evaluated.
**Effect of lung deflation with indacaterol plus glycopyrronium on ventricular filling in patients with hyperinflation and COPD (CLAIM): a double-blind, randomised, crossover, placebo-controlled, single-centre trial**

**Authors:** Hohlfeld JM et al.

**Reference:** Lancet Respir Med. 2018 Feb 21 [Epub ahead of print].

**URL:** https://www.ncbi.nlm.nih.gov/pubmed/29477448

**Comments:**

Pulmonary hyperinflation in COPD is associated with reduced biventricular end-diastolic volumes and increased morbidity and mortality. The combination of LABALAMA is effective in reducing hyperinflation but whether dual bronchodilation improves cardiac function is unknown. The authors did a double-blind, randomized, two-period crossover, placebo-controlled, single-centre study (CLAIM). Eligible participants were patients aged at least 40 years with COPD, pulmonary hyperinflation (RV >135%), a smoking history of at least ten pack-years, and airflow limitation (FEV1 <80% and FEV1/FVC < 0.7). Patients with stable cardiovascular disease were eligible, but those with arrhythmias, heart failure, unstable ischemic heart disease, or uncontrolled hypertension were not. The authors randomly assigned participants (1:1) to either receive a combined inhaled dual bronchodilator containing the LABA indacaterol (110 μg as maleate salt) plus the LAMA glycopyrronium (50 μg as bromide salt) once per day for 14 days, followed by a 14-day washout, then a matched placebo for 14 days, or to receive the same treatments in reverse order. The primary endpoint was the effect of indacaterol-glycopyrronium versus placebo on left-ventricular end-diastolic volume measured by MRI done on day 1 (visit 4) and day 15 (visit 5) in treatment period 1 and on day 29 (visit 6) and day 43 (visit 7) in treatment period 2 in the per-protocol population. The authors randomly assigned 62 eligible participants to treatment; 30 to indacaterol-glycopyrronium followed by placebo and 32 to placebo followed by indacaterol-glycopyrronium. After indacaterol-glycopyrronium treatment, left-ventricular end-diastolic volume increased from a mean 55·46 mL/m² (SD 15·89) at baseline to a least-squares (LS) mean of 61·76 mL/m² (95% CI 57·68-65·84), compared with a change from 56·42 mL/m² at baseline (13·54) to 56·53 mL/m² (52·43-60·62) after placebo (LS means treatment difference 5·23 mL/m² [95% CI 3·22 to 7·25; p<0·0001]). This is the first study to analyze the effect of LABALAMA combination therapy on cardiac function in patients with COPD and lung hyperinflation. The results are important because of the known association of cardiovascular impairment with COPD, and support the early use of dual bronchodilation in patients with COPD who show signs of pulmonary hyperinflation. Further large clinical trial to confirm the result of this study is needed.
Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials

Authors: Bafadhel M et al.


URL: https://www.ncbi.nlm.nih.gov/pubmed/29331313

Comments:
The peripheral blood eosinophil count might help identify those patients with COPD who will experience fewer exacerbations when taking ICS. Previous post-hoc analyses have proposed eosinophil cutoffs that are both arbitrary and limited in evaluating complex interactions of treatment response. The authors modelled eosinophil count as a continuous variable to determine the characteristics that determine both exacerbation risk and clinical response to ICS in patients with COPD. The authors analyzed data from three AstraZeneca randomized controlled trials of budesonide-formoterol in patients with COPD with a history of exacerbations and available blood eosinophil counts. 4,528 patients were studied. A non-linear increase in exacerbations occurred with increasing eosinophil count in patients who received formoterol alone. At eosinophil counts of $0.10 \times 10^9$ cells per L or more, a significant treatment effect was recorded for exacerbation reduction with budesonide-formoterol compared with formoterol alone (rate ratio 0.75, 95% CI 0.57-0.99; pinteraction=0.015). Interactions were observed between eosinophil count and the treatment effects of budesonide-formoterol over formoterol alone (pinteraction=0.0043) and pre-bronchodilator FEV1 (linear effect $p<0.0001$, pinteraction=0.067). Only eosinophil count and smoking history were independent predictors of response to budesonide-formoterol in reducing exacerbations (eosinophil count, pinteraction=0.013; smoking history, pinteraction=0.015). In patients with COPD treated with formoterol, blood eosinophil count predicts exacerbation risk and the clinical response to ICS. Although this was retrospective analysis, the result is very informative. Also, the result of this study is well compatible with previous analysis of fluticasone and beclomethasone study (Lancet Respir Med 2015; 3: 435-442., Am J Respir Crit Care Med 2015; 192: 523-525.). In patients with high blood eosinophil and history of frequent exacerbation, physicians should consider ICS containing regimen as first line treatment.
**Intensified Therapy with Inhaled Corticosteroids and LABA at the Onset of URTI to Prevent COPD Exacerbations- A Multicentre, Randomised, Double-blind, Placebo-controlled Trial**

Authors: Stolz D et al.


URL: https://www.ncbi.nlm.nih.gov/pubmed/29266965

Comments:
The authors aimed to evaluate whether intensified combination therapy with ICS/LABA, at the onset of URTI symptoms, decreases the incidence of COPD exacerbation occurring within 21 days of the URTI. 450 patients with stable, moderate to very severe COPD, were included in this investigator-initiated and driven, double-blind, randomized, placebo-controlled study. At inclusion, patients were assigned to open-labelled low maintenance dose ICS/LABA. Each patient was randomized either to intensified dose ICS/LABA or placebo and instructed to start using this medication only in case of an URTI, at the onset of symptoms, twice daily, for 10 days. The incidence of any exacerbation following a URTI was not significantly decreased in the ICS/LABA group, as compared to placebo (14.6% versus 16.2%, HR 0.77, 95%CI 0.46-1.33, P=0.321) but the risk of severe exacerbation was decreased by 72% (HR 0.28, 95%CI 0.11-0.74%, P=0.010). In the stratified analysis, effect size was modified by disease severity, FeNO and BODE score. Compared to the stable period, evidence of at least one virus was significantly more common at URTI, 10 days after URTI and at exacerbation. This study is very interesting and the result is informative. The onset of an URTI can indicate that an exacerbation will follow. However, unfortunately, there are no anti-viral therapies currently licensed for use at acute COPD exacerbations. This study provided good evidence that we may prevent COPD exacerbation after URTI by increase of ICS/LABA.

**Persistently elevated exhaled nitric oxide fraction is associated with increased risk of exacerbation in COPD**

Authors: Alcázar-Navarrete B et al.

Reference: Eur Respir J. 2018 Jan 18;51(1).

URL: https://www.ncbi.nlm.nih.gov/pubmed/29348180

Comments:
Preventing the occurrence of acute exacerbations of COPD (AECOPD) is a major therapeutic goal. The authors hypothesize that persistently increased levels of exhaled nitric oxide (FeNO) during follow-up can identify a group of COPD patients at higher risk of AECOPD.
To test this hypothesis, the authors measured FeNO levels prospectively in 226 clinically stable COPD outpatients at recruitment and during follow-up (at 6 and 12 months). Patients were stratified according to the number of visits with FeNO ≥20 ppb. FeNO was <20 ppb in all three visits in 44.2% of patients, 29.6% in visit 1 and 26.1% in visit 2 or 3. These three groups suffered progressively higher AECOPD rates during follow-up (0.67, 0.91 and 1.42, respectively, p<0.001). After adjusting for potential confounding variables, the hazard ratio for AECOPD was higher in the latter group (1.579 (95% CI 1.049-2.378), p=0.029). Likewise, time to first moderate and severe AECOPD was shorter in these patients. Finally, there was no relationship between FeNO levels and circulating eosinophils. Persistent FeNO levels ≥20 ppb in clinically stable COPD outpatients are associated with a significantly higher risk of AECOPD. This interesting study suggested that FeNO can be a potential biomarker to predict risk of exacerbation. Little study has showed the clinical efficacy of FeNO in COPD. This important study provided good rationale to use FeNO in clinical practice. Further clinical trial regarding the role of FeNO in COPD management is needed. Especially, whether patients with high FeNO will respond ICS treatment is needed.

Authors: Cabrera López C et al.
URL: https://www.ncbi.nlm.nih.gov/pubmed/29099607
Comments:
The GOLD document has modified the grading system directing pharmacotherapy, but how this relates to the previous one from 2015 and to comorbidities, hospitalizations, and mortality risk is unknown. The aim of this study was to evaluate the changes in the GOLD groups from 2015 to 2017 and to assess the impact on severity, comorbidities, and mortality within each group. The authors prospectively enrolled and followed, for a mean of 5 years, 819 patients with COPD. The authors determined anthropometrics, lung function (FEV1%), dyspnea score (mMRC), ambulatory and hospital exacerbations, and the BODE and Charlson indexes. The authors classified patients by the 2015 and 2017 GOLD ABCD system, and compared the differential realignment of the same patients. The authors related the effect of the reclassification in BODE and Charlson distribution as well as COPD and all-cause mortality between the two classifications. Compared with 2015, the 2017 grading decreased by half the proportion of patients in groups C and D (20.5% vs. 11.2% and 24.6% vs. 12.9%; P < 0.001). The distribution of Charlson also changed, whereas group D was higher than B in...
2015, they become similar in the 2017 system. In 2017, the BODE index and risk of death were higher in B and D than in A and C. The mortality risk was better predicted by the 2015 than the 2017 system. Compared with 2015, the GOLD ABCD 2017 classification significantly shifts patients from grades C and D to categories A and B. The new grading system equalizes the Charlson comorbidity score in all groups and minimizes the differences in BODE between groups B and D, making the risk of death similar between them. There has been a debate whether GOLD 2017 classification is better than 2015. The result of this study suggested that GOLD 2017 may be not better than 2015 in terms of predicting mortality.