Table C.10. Characteristics of the included studies in KQ 1d FeNO response to administration of bronchodilators (beta agonists and anticholinergics)

| Author, Year (ref) | Study Country, Study Design, Study Settings, Risk of Bias | FeNO and Comparisons | Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc) | Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test) | Medication (Frequency, Dose, Duration, etc.) | Asthma Outcomes | Test Findings (Mean, SD) | Conclusions |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Fuglsang, 1998 151 | Denmark, RCT with crossover, outpatient setting, low risk of bias. | FeNO, N= 22 | Mean age 11.6 years (7-15). | Measured by online chemiluminescence-model LR200, Logan Research, at 5-6 L/min | 3 weeks of inhaled 50 µg salmeterol BID, placebo or inhaled 200 µg budesonide BID. | There was no statistically significant difference in FeNO after salmeterol and placebo treatment, however, budesonide significantly decreased to normal level. | Endpoint FeNO salmeterol: 12.7.Placebo: 10.7.Budesonide: 5.2. | FeNO levels were unaffected by salmeterol treatment for 3 weeks but were significantly reduced during budesonide therapy.  |
| Spirometry, N= 22 |  | The terbutaline dose–response curve appeared flatter after the salmeterol period than after the placebo period for both FEV1 and FEF25-75. | FEV1 (% pred) mean difference Placebo 18%Salmeterol 2%FEF25-75% mean differencePlacebo 41%Salmeterol 4%. |
| Inoue, 2016152 | Japan, RCT, outpatient setting, Low risk of bias | FeNo, N=33 | Tulobuterol Patch (TP) group, N=16Mean age 56.7 years, 25% male, 6% ex-smoker, mean BMI 24.2 kg/m2 Salmeterol Inhaler (SI) group, N=17Mean age 49.2 years, 24% male, 29% ex-smoker, mean BMI 23 kg/m2  | FeNO was measured first using a chemiluminescence analyzer (NOA 280;Sievers Instruments, Boulder, CO, USA) according to the ATS at 50 mL/sec expiratory flow rare. | 12 weeks add-on treatment with either Tulobuterol Patch (TP) or Salmeterol Inhaler (SA) on ICS. | FeNO showed no statistically significant in both decreased after TP and increased after SA. | TP18.9 ppb (12.6-47.1) to 17.2 ppb (8.8-36.9)SA22.8 ppb (8.1-69) to 25.2 ppb(6.9-63.2) | Add-ontreatment of TP improved asthma control and health status, whereas SA improvedpulmonary function measures among patients with adult-onset mild-to- moderate asthma. |
| Spirometry, N=33 | Measured after FeNO according to the ATS standards using a ChestGraph HI-701 spirometer (Chest M.I., Tokyo, Japan) without taking a bronchodilator. | FEF25-75% was significantly improved in SA vs no improvement in TP. | TP2.8 L/s (0.92) to 2.61 L/s (0.83).SA2.48 L/s (1.19) to 2.73 L/s (1.25).  |
| Asthma control test (ACT), N = 33 | Five questions questionnaire, with the best score of 25. | ACT significantly improved after TP, while non-significant increased after SA was observed. | TP21 (5-25) to 24 (17-25). SA21 (10-25) to 23 (10-25). |
| Hoshino, 2016153 | Japan, RCT, outpatient setting, High risk of bias | FeNo= 53 | Group 1: add-on Tiotropium + ICS + LABA group, N= 25Mean age 57 years, 44% male, mean BMI 25.6 kg/m2, 72% atopic patientsGroup 2: ICS + LABA group, N = 28Mean age 53 years, 56% male, mean BMI 24.1 Kg/m2, 71% atopic patients | Measured by electrochemical reaction by using a portable nitric oxide analyzer (NioxMino; Aerocrine, Solna, Sweden) at an exhalation flow rate of 50 mL/sec. | (Group1) 48 weeks of 5 mg daily Tiotropium add-on to maintenance therapy in asthma with ICS plus LABA (delivered through the RespimatSoftMist inhaler [Boehringer Ingelheim, Ingelheimam Rhein, Germany]) or no add-on (group 2). | No significant change in FeNO was observed in add-on or no add-on groups from baseline to week 48. | Group1 -5.0 (SD:4.6)Group2-1.6 (SD:6.1) | The addition of once-daily tiotropium to maintenance therapy improved airflow limitation and reduced airwayT. A triple combination of tiotropium and ICS plus LABA may have additive protective effects of bronchodilation and remodeling. |
| Spirometry =53 | Using computed spirometry. Predicted values for forced vital capacity and FEV1 were calculated by using the formula proposed by the Japanese Respiratory Society. | A significant difference in change in FEV1% predicted was observed between the two groups. | Group1 change in FEV1% pred 3.4 (SD:3.1)Group2 0.8 (SD:3.4) |
| Asthma Quality of Life Questionnaire (AQLQ), N=53 | A 32 items questionnaire covers symptoms, activities, emotions, and environment by using a seven- point scale. A change of >0.5 points represents a clinically meaningful improvement. | Significantly better scores for symptoms and emotions in the group 1unlike no improvement in group. The difference in symptom score between the groups was statistically significant.  | Group1 Change in symptom 0.5 Change in emotion 0.2 Group2Change in symptom 0.2 Change in emotion 0.1 |
| Yates, 1997 154 | United Kingdom, RCT with cross-over, outpatient, low risk of bias. | FeNO, N= 20 | Talking ICS (N= 10); mean age 30.1 years (21-39), 70% male, 90% atopic.Placebo (N= 10); mean age 29.6 years (22-63), 60% male, 80% atopic. | using an online chemiluminescence analyser (Dasibi Environmental Corporation Model, Glendale, CA, USA), at 1 L/min. | One week of nebulized salbutamol (5 mg), added to inhaled glucocorticosteroids (ICS) or placebo.  | Salbutamol added to inhaled ICS result in significant increase in FeNO comparted when added to placebo where shows no difference.  | Talking ICS124 ppb (SEM: 38) to 165 ppb (SEM: 85).Placebo205 ppb (SEM: 37) to 204 ppb (SEM: 44) | Single high dose salbutamol did not increase exhaled nitric oxide in asthmatics not taking inhaled glucocorticosteroids. |
| Spirometry. N= 20 | Using a dry wedge spirometer (Vitalograph, Buckingham, UK). | Salbutamol showed an improvement in FEV1 (5 pred) when added to inhaled ICS or placebo. | Talking ICS91 (SD: 6) to 98 (SD: 5).Placebo94 (SD: 5) to 104 (SD: 5) |

FeNO: fraction exhaled nitric oxide; FEF25–75: forced expiratory flow at 25–75% of forced vital capacity; FEV1: forced expiratory volume in the first second; FEV1% pred: forced expiratory volume in the first second percentage predicted; FVC: forced vital capacity; ICS: inhaled corticosteroid; RCT: randomized clinical trial; SD: standard deviation; SEM: standard error of the mean.