# 1. ABSTRACT

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| **Name of company:** Boehringer Ingelheim | | | |
| **Name of finished medicinal product:** Spiriva | | | |
| **Name of active ingredient:** Tiotropium bromide | | | |
| **Report date:** 31 May 2016 | **Study number:** 205.526 | **Version/Revision:** Version 1.0 | **Version/Revision date:** N/A |
| **Title of study:** | Combined bronchodilators in chronic obstructive pulmonary disease and the risk of adverse cardio-pulmonary events: A population-based observational study | | |
| **Keywords:** | Long-acting bronchodilators; COPD; pharmacoepidemiology; cardiovascular risk; cohort study; | | |
| **Rationale and background:** | Long-acting bronchodilator medications, that include long-acting beta$_2$-agonists (LABAs) and the long-acting anticholinergic tiotropium, have become central maintenance therapy to the management of COPD. Since these long-acting bronchodilators are often used concurrently, the potential cardio-pulmonary risk arising from their concurrent use needs study. Moreover, it remains unclear from both randomized trials and observational studies whether and to what extent the initiation of monotherapy with each of the long-acting bronchodilators is associated with an increased risk of cardio-pulmonary events. | | |
| **Research question and objectives:** | **Primary objective**: To assess whether adding a second long-acting bronchodilator, either a long-acting beta$_2$-agonist (LABA) to tiotropium use, or vice versa adding tiotropium to LABA use, increases the risk of acute myocardial infarction (AMI), stroke, heart failure, arrhythmia and community acquired pneumonia in patients with COPD, relative to monotherapy.<br><br>**Secondary objective**: To assess whether treatment initiation with tiotropium monotherapy, compared with initiation with LABA monotherapy, increases the incidence of these cardiovascular and pulmonary events.<br><br>**Tertiary objective**: To assess whether use of tiotropium and LABAs, alone and concurrently, increases the incidence of these cardiovascular and pulmonary events, relative to non-use. | | |
| **Study design:** | Population-based cohort studies, using both propensity score matched cohort designs (objective 1 and 2) and nested case-control analyses (objective 3) to address the three objectives. | | |
| **Setting:** | The study was conducted in a general practice setting, the Clinical Practice Research Datalink (CPRD) | | |
| **Subjects and study size, including dropouts:** | The base cohort included 115,397 new users of tiotropium or a LABA between September 25, 2003, and August 31, 2013, aged 55 years or older, was used for the analysis of the AMI, stroke and heart failure outcomes. The base sub-cohort of 70,550 new users with data linked to the Hospital Episodes Statistics database was used for the arrhythmia and pneumonia outcomes. | | |

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| **Variables and data sources:** | The exposures were based on prescriptions for the two long-acting bronchodilators under study, namely LABA and tiotropium. The cardiovascular outcomes of myocardial infarction, heart failure and stroke were identified from GP diagnoses in the full base cohort. The outcomes of arrhythmia and pneumonia were based on hospitalization diagnoses in the sub-cohort with linkage to hospital statistics. Covariates included demographics, lifestyle variables, cardiovascular and other co-morbidity (e.g. asthma), co-medications, and measures of COPD severity. | | |
| **Results:** | For the primary objective, the hazard ratios associated with adding a second long-acting bronchodilator (tiotropium or a LABA +/- ICS), relative to remaining on a single long-acting bronchodilator (tiotropium or a LABA +/- ICS), from the as-treated analysis, were, for AMI 1.12 (95% CI: 0.92-1.37), for stroke 0.87 (95% CI: 0.69-1.10) and for arrhythmia 1.05 (95% CI: 0.81-1.36). For heart failure, the hazard ratio was 1.16 (95% CI: 1.03-1.30) and for pneumonia 1.35 (95% CI: 1.23-1.50).<br>For the secondary objective, the hazard ratios associated with tiotropium initiation (+/- ICS), relative to LABA initiation (+/- ICS) were for AMI 1.10 (95% CI: 0.88-1.38), for stroke 1.02 (95% CI: 0.78-1.34), for arrhythmia 0.81 (95% CI: 0.60-1.09), heart failure 0.90 (95% CI: 0.79-1.02) and for pneumonia 0.81 (95% CI: 0.72-0.92).<br>For the tertiary objective, the rate ratio associated with current use of tiotropium and LABA (both +/- ICS)used concurrently, compared with non-use was, for AMI 1.17 (95% CI: 1.02-1.34), for heart failure 1.47 (95% CI: 1.33-1.64) and for pneumonia 1.86 (95% CI: 1.72-2.02), while for stroke it was 0.93 (95% CI: 0.80-1.08) and for arrhythmia 1.16 (95% CI: 0.97-1.39). | | |
| **Discussion:** | In all, this large real world setting study of the treatment of COPD suggests that the addition of a second long-acting bronchodilator, either a long-acting $beta_2$-agonist (LABA) to tiotropium use, or vice versa adding tiotropium to LABA use (both +/- ICS), as recommended by COPD treatment guidelines when the disease worsens, does not appear to lead to significant increases in cardiovascular and cerebrovascular risks, except perhaps for a small increase in the risk of heart failure. The latter warrants continued monitoring since this elevated risk of heart failure with the addition of a second long-acting bronchodilator was particularly observed among those patients with no history of heart failure before treatment initiation (hazard ratio 1.21; 95% CI: 1.05-1.39), but not among those with a history of heart failure (hazard ratio 1.04; 95% CI: 0.85-1.26). However, the latter group was smaller and the upper 95% confidence limit suggests that the data are compatible with an increase in the risk.<br>A pooled safety analysis of the tiotropium HandiHaler and Respimat randomized, double-blind, parallel-group, placebo-controlled trials, in patients with COPD found that patients on tiotropium had a decreased risk of cardiac failure (RR 0.81;95% CI: 0.69, 0.96) and of myocardial infarction (RR 0.85;95% CI: 0.67, 1.09). [Halpin et al, 2015; P15-01613] However, this pooled analysis did not | | |

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| | provide a stratified analysis by concurrent use of a LABA (over 37% of all patients) to assess the effect of adding tiotropium to the LABA on these outcome events.<br><br>Additionally, initiating treatment with tiotropium or a long-acting beta$_2$-agonist (both +/- ICS) as first-line maintenance therapy in COPD, without adding a second long-acting bronchodilator, (second objective) appears to have comparable cardiovascular and cerebrovascular safety profiles.<br>However, the initiation of maintenance monotherapy with tiotropium compared with monotherapy with a long-acting beta$_2$-agonist significantly reduced the risk of pneumonia. This lower risk of pneumonia with tiotropium was likely a direct result of the elevated risk of pneumonia associated with the inhaled corticosteroids contained in most LABA inhalers. An excess risk was not observed with tiotropium or with long-acting beta$_2$-agonists that do not contain an inhaled corticosteroid (HR 0.81; 95% CI: 0.59-1.11).<br>The findings for the tertiary objective aimed to compare the use of long-acting bronchodilators with non-use over the longer term are less reliable due to the potential for residual confounding. This is particulalry so since the cohort started with patients who all initiated treatment with a long-acting bronchodilator and the reference group, defined by non-use of a long-acting bronchodilator during an entire year, represents patients that are quite different from those who continued to use and needed long-acting bronchodilators. | | |
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