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# Risk of Severe Cardiovascular Events From Add-On Tiotropium in Chronic Obstructive Pulmonary Disease

Jun-Ting Liou, MD; Chen Wei Lin, BS; Chen-Liang Tsai, MD; Yun-Han Wang, MS, BPharm; Jyun-Heng Lai, MS, BPharm; Yu-Juei Hsu, MD, PhD; and Meng-Ting Wang, PhD

## Abstract

**Objective:** To examine the risk of cardiovascular disease (CVD) from tiotropium added to inhaled long-acting $\beta_2$ agonists (LABAs) and inhaled corticosteroids (ICSs) in a nationwide population with chronic obstructive pulmonary disease (COPD).

**Patients and Methods:** This nested case-control study included 65,966 patients with COPD treated with LABAs and ICSs identified from the Taiwan nationwide health care claims database from January 1, 2007, through June 30, 2011. Cases were all patients with a first primary diagnosis of ischemic heart disease, heart failure, stroke, or arrhythmia from inpatient or emergency care settings during follow-up, and each was matched with 4 disease risk score–matched controls from risk sets. The use of tiotropium in the year before the index/event date was measured, stratified by duration since therapy initiation, concomitant COPD medications, and dosage form. Conditional logistic regression models were used to estimate odds ratios of the CVD risk from add-on tiotropium therapy.

**Results:** From the study cohort, with a mean age of 70.3 years (interquartile range, 61.8-79.4 years), 3188 CVD cases (incidence rate, 6.2 [95% CI, 6.0-6.4] cases per 100 person-years) and 12,349 matched controls were identified. The new use of tiotropium was associated with a 1.88-fold (95% CI, 1.44-2.46) increased CVD risk within 30 days of therapy initiation, and the association was sustained up to 60 days after treatment initiation (adjusted odds ratio, 1.71; 95% CI, 1.08-2.70). The risk persisted across all tiotropium regimens, with a case-crossover analysis, and in comparison with new add-on theophylline therapy.

**Conclusion:** Tiotropium newly added to LABA/ICS combination therapy was associated with an increased cardiovascular risk in patients with COPD.

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Chronic obstructive pulmonary disease (COPD) is a progressive and irreversible airway inflammatory disease that poses a major threat to public health and presently affects 380 million people worldwide.[1] This disease is ranked as the fourth leading cause of death, with an annual death rate of 4.8%,[2] and is projected to be the third leading cause of death by 2030.[3]

The triple inhalation therapy of long-acting $\beta_2$ agonists (LABAs) plus long-acting antimuscarinic agents (LAMAs) plus inhaled corticosteroids (ICSs) remains the cornerstone of treatment for patients with severe COPD. Before 2017, the Global Initiative for Chronic Obstructive Lung Disease treatment guidelines suggested the addition of tiotropium, the most commonly prescribed LAMA, to LABA/ICS combination therapy in patients with the most severe COPD (group D patients).[4] The new 2017 Global Initiative for Chronic Obstructive Lung Disease guidelines advocate the use of LABA/LAMA therapy over LABA/ICS therapy as the initial dual therapy in group D patients but still recommends that patients with a high blood eosinophil count or asthma-COPD overlap syndromes be prescribed LABA/ICS combination therapy.[5] Nonetheless, when both combination therapies fail to control the disease, escalation to

From the Division of Cardiology (J.-T.L.), Division of Pulmonary and Critical Care (C.-L.T.), Division of Nephrology, Department of Medicine (Y.-J.H.), Tri-Service General Hospital, School of Pharmacy (C.W.L., Y.-H.W., J.-H.L., M.-T.W.), and Graduate Institutes of Medical Sciences and Biochemistry (Y.-J.H.), National Defense Medical Center, Taipei, Taiwan, Republic of China.

triple therapy of ICS/LABA/LAMA is recommended.[5] Regardless of the suggested conditions for the use of triple therapy, in the present clinical setting, the widespread use of LAMA/LABA/ICS therapy for the treatment of COPD has been documented in several countries, ranging from 21% to 45%.[6-8] Notably, the addition of tiotropium to a LABA/ICS combination regimen is the primary pathway to triple therapy,[6] but little is known about the safety of the use of this add-on drug.

Tiotropium use has been recently linked to cardiovascular risk, despite conflicting evidence. Several studies[9-12] have reported 1.24- to 1.80-fold increased risks of cardiovascular adverse events, but neutral findings[10,13-15] have also been reported, including in the 4-year Understanding Potential Long-Term Impacts on Function with Tiotropium trial.[16] The discrepancies probably arose because the studies, including the Understanding Potential Long-Term Impacts on Function with Tiotropium trial, lacked sufficient power,[10,13-17] focused on a mixed population with respiratory tract disease[11] or strictly selected patients with COPD,[9] and included prevalent tiotropium users who might have developed tolerance to the risk of cardiovascular disease (CVD).[10,13,15-17] More importantly, none of the studies specified tiotropium use as an add-on therapy, which could lead to potential confounding by a differential underlying disease severity or concomitant bronchodilator drug use.

We aimed to assess whether the addition of tiotropium to a LABA/ICS combination regimen in patients with COPD was associated with an increased risk of CVD as well as to further examine whether the risk varied by recency, dosage form of tiotropium, and concomitant use of other COPD medications.

## PATIENTS AND METHODS

### Data Source and Setting

This study was conducted by analysis of Taiwan's National Health Insurance Research Database (NHIRD) from January 1, 2007, through June 30, 2011, which contained details of clinical encounters including medical diagnoses, procedures, and dispensed medications in inpatient, outpatient, and emergency care settings in the compulsory and universal National Health Insurance (NHI) program, which covers more than 99% of the 23 million inhabitants of Taiwan. The quality of data contained in NHIRD is ensured by quarterly accreditation by the National Health Insurance Administration,[18] and the claims records have been reported to be concordant with patient self-reports.[19] NHIRD is often analyzed to assess drug safety, including drug-related adverse cardiovascular events.[20] All the data analyzed in the present study were double anonymized. This study was exempt from a full review by the Institutional Review Board of Tri-Service General Hospital, National Defense Medical Center (B-102-19).

### Cohort Selection

We identified all patients who were 40 years or older and had made an inpatient or outpatient visit for COPD (*International Classification of Diseases, Ninth Edition* [*ICD-9*] codes 491, 492, 496), accompanied by a prescription-filling record for both a LABA and an ICS at the visit from January 1, 2008, through June 30, 2011. The first LABA and ICS combination prescription-filling record marked the cohort entry date. Continuation of LABA/ICS combination therapy was defined on the basis of a 90-day grace period between successive combination prescriptions, with a 3-month extended observation period, if discontinued. Patients with lung cancer, congenital heart disease, previous hospitalization or emergency department (ED) visits with a primary diagnosis of CVD, a lack of a full year of continuous NHI coverage, and any tiotropium prescription filled in the year before cohort entry were excluded. The study cohort was followed up until an inpatient or ED primary diagnosis of CVD, NHI withdrawal, discontinuation of LABA/ICS therapy, death, or the end of the study (December 31, 2011), whichever occurred first. Patient mortality in the NHIRD was determined using a previously reported approach.[21]

### Case Identification and Control Selection

We identified cases as all patients who had a first-time inpatient or ED visit with a primary diagnosis of coronary heart disease (*ICD-9* codes 410-414), heart failure (*ICD-9* code 428), ischemic stroke (*ICD-9* codes 433-434), or cardiac arrhythmia (*ICD-9* code 427)