Hospitalization for Heart Failure Among Patients Using Aclidinium Bromide and Other COPD Medications: A Post-Authorization Safety Study in CPRD

Estel Plana,[1] Elena Rivero-Ferrer,[1] Jaume Aguado,[1] Núria Saigí-Morgui,[1] Javier Nuevo,[2] Sami Z Daoud,[3] Alejhandra Lei,[4] Susana Perez-Gutthann,[1] Cristina Rebordosa[1]

[1]RTI Health Solutions, Barcelona, Spain; [2]AstraZeneca, Madrid, Spain; [3]AstraZeneca, Gaithersburg, United States; [4]AstraZeneca, Barcelona, Spain

DISCLOSURES

The study was funded by AstraZeneca under a contract with RTI Health Solutions (RTI-HS) granting the research team independent publication rights. RTI-HS is a unit of RTI International, a non-profit organization that conducts work for government, public, and private organizations, including pharmaceutical companies such as AstraZeneca. As an RTI-HS employee, SPG has also participated in scientific advisory boards that were funded by pharmaceutical companies. JN, SZD, and AL are employees of AstraZeneca.

BACKGROUND

- Aclidinium bromide is an inhaled long-acting anticholinergic (LAMA) approved in Europe in 2012 as a maintenance bronchodilator treatment to relieve symptoms in adults with chronic obstructive pulmonary disease (COPD).
- This study is part of a PASS (post-authorization safety study) program to evaluate potential cardiovascular safety concerns, based on concerns about the use of LAMA medications, included in the aclidinium risk management plan EUPAS13616.[1]

OBJECTIVE

- To compare the risk of first ever hospitalization for heart failure (HF) among patients without prior hospitalization for HF in patients with COPD initiating treatment with aclidinium bromide and other selected COPD medications with the risk in patients with COPD initiating treatment with long-acting beta2-agonists (LABA)
- To evaluate the effect of duration of use
- To conduct sensitivity and subgroup analyses

METHODS

- This non-interventional database cohort study included patients with COPD aged 40 years or older starting treatment with aclidinium (monotherapy or in fixed-dose combination with formoterol), tiotropium, other LAMA (glycopyrronium or umeclidinium), LAMA/LABA, LABA/inhaled corticosteroids (LABA/ICS), or LABA from the General Practitioner Online Database (GOLD) of Clinical Practice Research Datalink (CPRD) in the United Kingdom, from September 2012 through June 2017. For practices where linkage was available, the study also included information from the Office for National Statistics (ONS) and the Hospital Episode Statistics database (HES).
- Hospitalizations for HF events were validated, and the main analysis included all cases identified through HES primary discharge diagnosis or through GOLD diagnosis code and a hospitalization code plus only confirmed cases identified through HES secondary discharge diagnosis. Validation methods and results are presented in a separate poster.[2]
- Crude incidence rates (IRs), incidence rate ratios (IRRs), and adjusted IRRs of first ever hospitalization for HF were estimated for current use of each study medication vs. current use of LABA. IRRs were also estimated for current single use and current multiple use and for short (< 6 months) and long (≥ 6 months) duration of current use of the study medications.
- Adjusted IRRs were estimated using Poisson regression models adjusting for age, sex, COPD severity, prior outpatient diagnosis of congestive HF, diuretics, ICS, asthma, and calendar year at start date.
- Several subgroup and sensitivity analyses were conducted on exposure, outcome, and data source.

RESULTS

- Distributions of age, sex, race, smoking status, body mass index, alcohol abuse, and deprivation index were similar across all the study medications. According to the COPD severity GOLD 2016 definition (Figure 1), users of aclidinium were the most severe patients and users of LABA were the least severe patients.
- See the main results as well as subgroup and sensitivity analyses in Table 1 and Figures 2-4.

Figure 1. Distribution of COPD Severity (GOLD Classification) by Study Medication

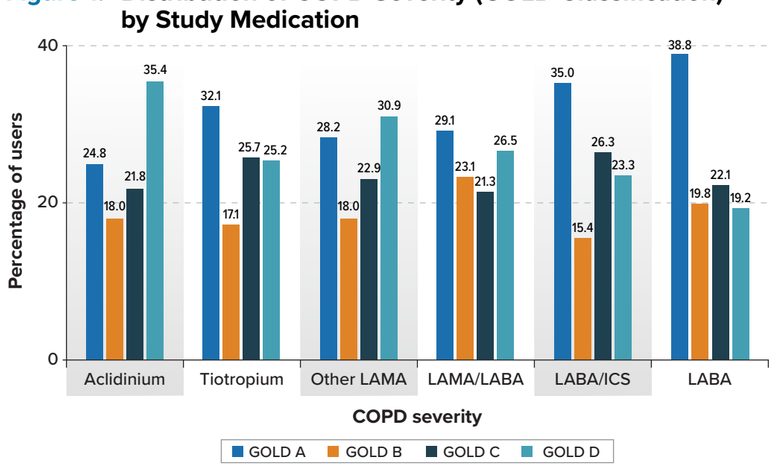
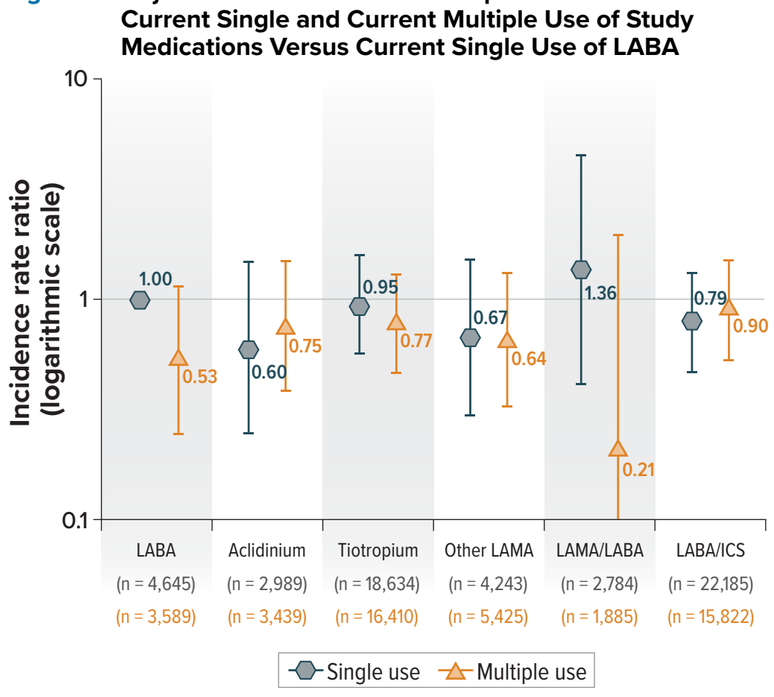
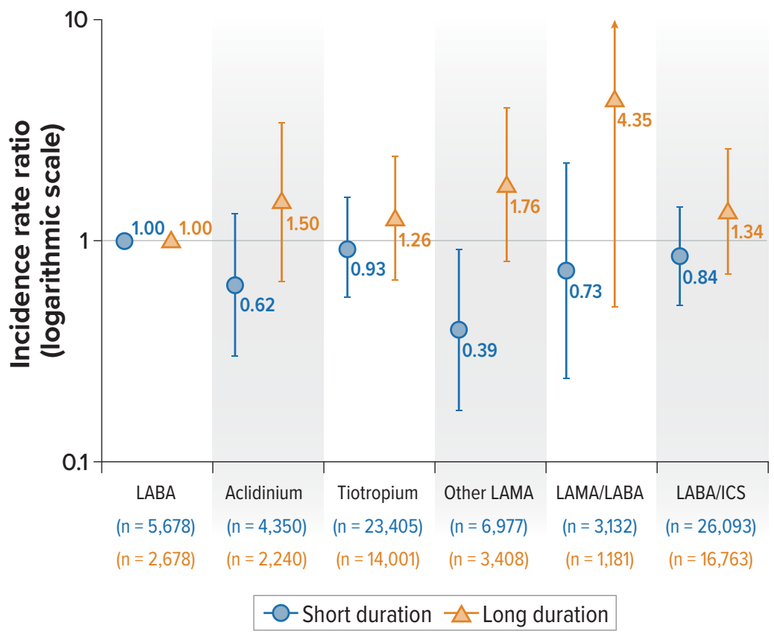


Figure 2. Adjusted IRRs of First Ever Hospitalization for HF for Current Single and Current Multiple Use of Study Medications Versus Current Single Use of LABA



Note: The reference category for all of the study medications is current single use of LABA without switching (no recent use of other study medications). Overall current single use refers to current use with and without switching.

Figure 3. Adjusted IRR of First Ever Hospitalization for HF by Short and Long Duration of Current Use of Study Medications Versus Current Short and Long Duration of LABA Use



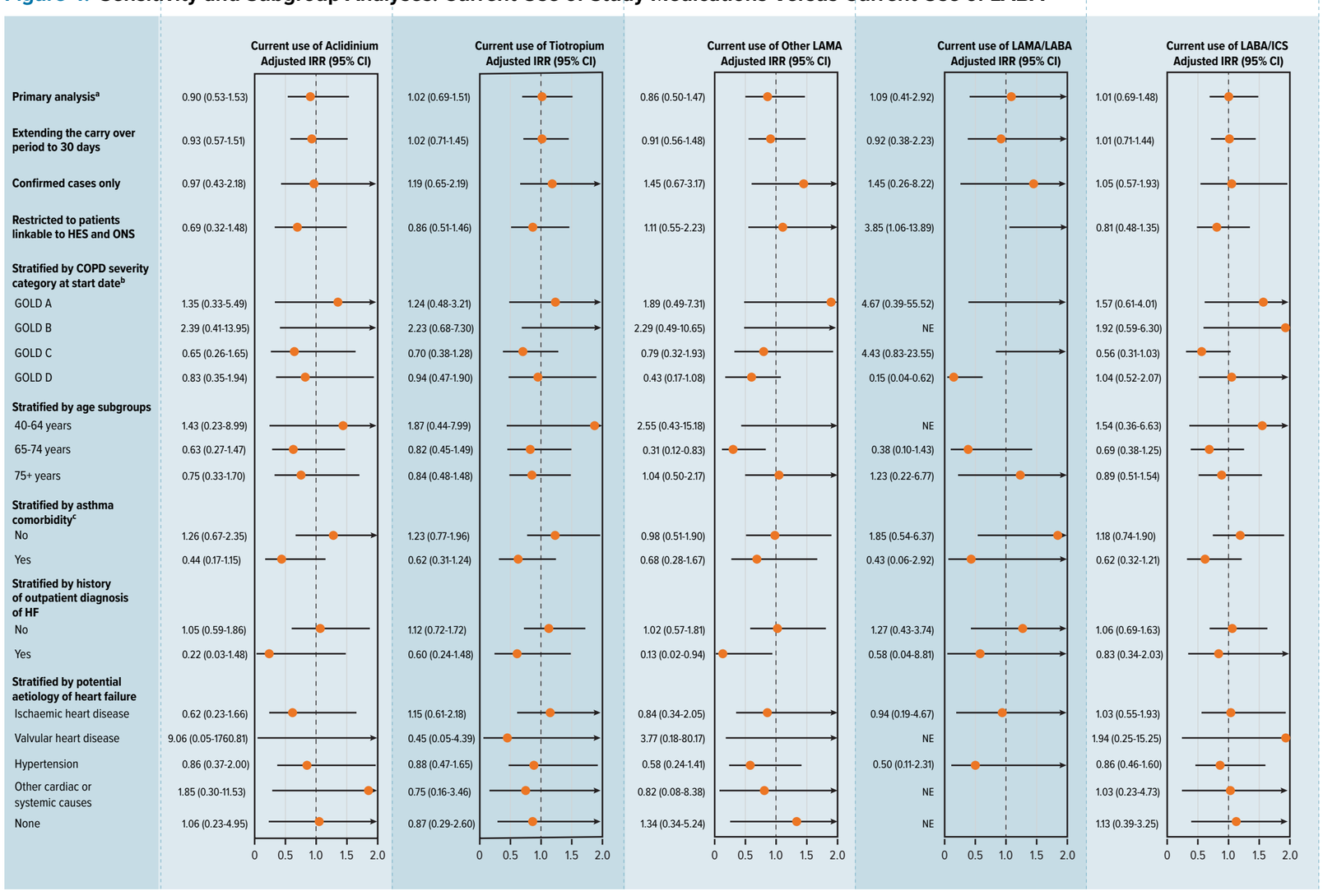
Note: The reference category for short duration was short duration of current use of LABA. The reference category for long duration was long duration of current use of LABA.

Table 1. Crude IRs and Crude and Adjusted IRRs for First Ever Hospitalization for HF Comparing Current Use of Each Study Medication With Current Use of LABA

Current Use	Aclidinium (N = 4,350)	Tiotropium (N = 23,450)	Other LAMA (N = 6,977)	LAMA/LABA (N = 26,093)	LABA/ICS (N = 5,678)
Number of events	36	186	40	13	213
PYs	3,783	24,490	5,036	1,571	29,036
IR per 1000 PY (95% CI)	9.52 (6.66, 13.17)	7.59 (6.54, 8.77)	7.94 (5.67, 10.82)	8.27 (4.41, 14.15)	7.34 (6.38, 8.39)
Crude IRR (95% CI)	1.38 (0.85, 2.23)	1.10 (0.75, 1.62)	1.15 (0.72, 1.84)	1.20 (0.62, 2.29)	1.06 (0.72, 1.55)
Adjusted IRR (95% CI)	0.90 (0.53, 1.53)	1.02 (0.69, 1.51)	0.86 (0.50, 1.47)	1.09 (0.41, 2.92)	1.01 (0.69, 1.48)

CI = confidence interval; PY = person-year.

Figure 4. Sensitivity and Subgroup Analyses: Current Use of Study Medications Versus Current Use of LABA



GOLD = Global Initiative for Chronic Obstructive Lung Disease; NE = nonevaluable.

[a] All models were adjusted by age, sex, COPD severity, prior outpatient diagnosis of congestive heart failure, diuretic use, ICS use, asthma, and calendar year at start date unless one of these variables was used for stratification.

[b] As measured through GOLD 2016 severity categories at the start date.

[c] With current asthma (i.e., at least one asthma diagnosis recorded within 5 years before the start date).

CONCLUSIONS

This study indicates that the use of aclidinium, tiotropium, other LAMA, LAMA/LABA, or LABA/ICS is not associated with an increased risk of congestive HF compared with the use of LABA.

The ongoing cardiovascular PASS program—which includes other substudies evaluating mortality, stroke, myocardial infarction, and arrhythmias—will provide further insight on the cardiovascular safety of aclidinium and other COPD medications.

REFERENCES

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2. Saigí-Morgui N, Rebordosa C, Bui C, et al. A validation exercise: identifying hospitalizations for heart failure among patients with COPD in CPRD. Poster presented at the 35th International Conference on Pharmacoepidemiology & Therapeutic Risk Management; August 24-28, 2019. Philadelphia, PA.

CONTACT INFORMATION

Estel Plana, MSc
RTI Health Solutions

Av. Diagonal 605, 9-1
08028, Barcelona, Spain

E-mail: eplana@rti.org

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