Are Aclidinium and Aclidinium/Formoterol Used According to Their Approved Indication in Europe? Results of a Multicountry Drug Utilization Postauthorization Safety Study

Elena Rivero-Ferrer,[1] Anna Julia Witzleb,[2] Morten Olesen,[3] Estel Plana,[1] Jaume Aguado,[1] Núria Saigí,[1] Annalisa Rubino,[4] Sami Z Daoud,[5] Alejhandra Lei,[6] Susana Perez-Gutthann,[1] Tania Schink,[2] Nina Sahlertz Kristiansen,[3] Anton Pottegård,[3] Cristina Rebordosa[1]

[1]RTI Health Solutions, Barcelona, Spain; [2]Leibniz Institute for Prevention Research and Epidemiology–BIPS, Bremen, Germany; [3]University of Southern Denmark, Odense, Denmark; [4]BioPharmaceuticals R&D, AstraZeneca, Cambridge, United Kingdom; [5]BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, United States; [6]BioPharmaceuticals R&D, AstraZeneca, Barcelona, Spain

DISCLOSURES

Study funded by AstraZeneca under a contract granting the research team independent publication rights. RTI Health Solutions, the Leibniz Institute for Prevention Research and Epidemiology, and the University of Southern Denmark receive institutional funding for projects from public and private entities. AR, SZD, and AL are employees of AstraZeneca.

BACKGROUND

- Aclidinium bromide was approved in the European Union for the treatment of chronic obstructive pulmonary disease (COPD) in adult patients in 2012 and in a fixed-dose combination with formoterol in 2014.
- As part of the pharmacovigilance plan, a multi-database drug utilization study has been conducted in the United Kingdom (UK), Denmark, and Germany (EU PAS Register EUPAS6559).

OBJECTIVES

- To evaluate the potential off-label use of aclidinium and aclidinium/formoterol
- To describe the characteristics of new users of study medications in the UK, Denmark, and Germany

METHODS

- An observational cohort study was conducted in new users of aclidinium bromide, aclidinium/formoterol, and other COPD medications in the UK Clinical Practice Research Datalink (CPRD GOLD, January 2015-December 2017), the Danish National Health Databases (March 2015-December 2017), and the German Pharmacoepidemiological Research Database (GePaRD, February-December 2015).
- Other COPD medications included in the study were:
  - Tiotropium
  - Other long-acting anticholinergics (LAMA): glycopyrronium bromide, umeclidinium
  - LAMA/long-acting beta-2 agonists (LABA): glycopyrronium/indacaterol, umeclidinium/vilanterol
  - LABA: formoterol, salmeterol, indacaterol, olodaterol
  - LABA/inhaled corticosteroid (ICS): formoterol/budesonide, formoterol/beclomethasone, formoterol/mometasone, formoterol/fluticasone, salmeterol/fluticasone propionate, vilanterol/fluticasone
- Patients with COPD were identified through Read codes in CPRD and *International Classification of Diseases, 10th Edition* (ICD-10) hospital discharge codes in Hospital Episode Statistics. COPD diagnoses were identified in the inpatient and outpatient databases using ICD-10 codes in Denmark and ICD-10-GM codes in GePaRD.
  - ICD-10 codes were J40 to J42 Chronic bronchitis, J43 Emphysema, and J44 Other COPD.
- On-label use was defined as use in adults with a diagnosis of COPD with or without asthma.
- Off-label use was defined as use in patients aged < 18 years or use in patients with a recorded diagnosis of asthma without a COPD diagnosis.
- Absence of a recorded diagnosis of COPD and asthma was classified as unknown indication.
- Severity of COPD was classified as mild, moderate, severe, and very severe (category not evaluated in GePaRD), according to an adapted validated algorithm.[1]
- Descriptive statistics were performed.

RESULTS

Table 1. Selected Characteristics of New Users of the Study Medications in Adults Aged 18 Years or Older, by Data Source, Country

Age and Lifestyle Characteristics	CPRD, UK	National Health Databases, Denmark	GePaRD, Germany
Number of new users			
Aclidinium	4,871	2,831	9,954
Aclidinium/formoterol	2,153	2,586	10,067
Tiotropium	21,959	45,201	35,458
Other LAMA	12,856	7,655	5,911
LAMA/LABA	7,272	40,517	20,417
LABA	7,335	40,653	45,174
LABA/ICS	77,181	132,180	251,705
Age, median (years)			
Aclidinium	69	69	67
Aclidinium/formoterol	70	71	68
LAMA medications, range	69-70	69-71	67-69
LABA, LABA/ICS	63, 56	67, 59	63, 53
Current smoking,[a] %			
Aclidinium	38.1	20.1	22.4
Aclidinium/formoterol	36.0	23.0	28.0
LAMA medications, range	36.0-39.9	20.1-23.0	21.9-28.0
LABA, LABA/ICS	26.8, 23.1	15.5, 10.7	15.6, 7.9
Obesity,[b] %			
Aclidinium	30.3	9.5	21.2
Aclidinium/formoterol	30.2	7.7	19.6
LAMA medications, range	29.6-30.3	7.6-9.5	19.6-22.2
LABA, LABA/ICS	29.1, 29.7	7.9, 9.6	19.3, 15.5
Alcohol abuse[c]			
Aclidinium	3.6	14.8	5.3
Aclidinium/formoterol	3.9	14.2	6.1
LAMA medications, range	3.6-4.1	13.5-15.4	5.2-6.6
LABA, LABA/ICS	3.4, 2.7	13.8, 15.5	4.1, 2.1

[a] Smoking status was defined based on the use of smoking-cessation drugs in Denmark and in GePaRD. In GePaRD, recorded diagnoses related to severe smoking were also used.

[b] Obesity is defined based on diagnosis in Denmark and based on diagnosis and use of medication for obesity in GePaRD.

[c] Alcohol abuse is defined based on the presence of diagnoses for alcohol abuse, dispensings of medications indicated for treatment of alcohol abuse, and related conditions in Denmark and in GePaRD; it is also based on consumption of units/day indicating heavy or very heavy drinking in the CPRD.

Table 2. Most Frequent Comorbidities in New Users of the Study Medications, Adults Aged 18 Years, by Study Medication and Data Source, Country

Data Source and Baseline Comorbidity	Aclidinium %	Aclidinium/ Formoterol %	LAMA Medications (range) %	LABA, LABA/ICS %
CPRD, UK	**(N = 4,871)**	**(N = 2,153)**	**(N = 2,153-21,959)**	**(N = 7,335, 77,181)**
Hypertension	50.9	52.5	49.5-52.5	40.4, 33.1
Depressive disorders	42.9	39.1	39.1-42.9	39.1, 38.4
Obesity	33.6	33.2	32.8-34.8	36.5, 39.2
Urinary tract infection	25.8	24.8	24.8-28.1	27.1, 26.6
Ischemic heart disease	21.8	21.0	20.8-21.8	13.9, 10.9
Charlson Comorbidity Index ≥ 3	23.5	21.6	21.0-25.2	16.6, 14.6
National Health Databases, Denmark	**(N = 2,831)**	**(N = 2,586)**	**(N = 2,586-45,201)**	**(N = 40,653, 132,180)**
Hypertension	69.0	72.6	69.0-73.2	60.0, 48.9
Urinary tract infection	47.8	46.6	46.6-49.3	46.4, 46.0
Depressive disorders	47.7	48.6	47.7-49.4	42.7, 39.4
Pneumonia	28.4	28.2	23.3-31.1	18.3, 18.2
Ischemic heart disease	23.1	23.3	21.7-24.1	17.6, 13.8
Charlson Comorbidity Index ≥ 3	27.4	30.0	24.8-31.0	19.3, 16.5
GePaRD, Germany	**(N = 9,954)**	**(N = 10,067)**	**(N = 5,911-35,458)**	**(N = 45,174, 251,705)**
Hypertension	66.3	67.0	66.3-68.9	56.2, 40.5
Benign prostatic hyperplasia[b]	28.8	26.4	26.4-28.8	22.8, 14.9
Ischemic heart disease	26.9	26.3	26.3-29.9	19.1, 10.5
Depressive disorders	25.1	23.9	23.9-26.8	23.6, 20.4
Diabetes	24.5	24.6	24.5-27.6	20.4, 13.1
Charlson Comorbidity Index ≥ 3	41.8	43.7	41.8-49.8	33.9, 19.6

[a] Percentage among males.

Figure 1. Severity of COPD in New Users of Study Medications Aged 40 Years or Older, by Data Source, Country

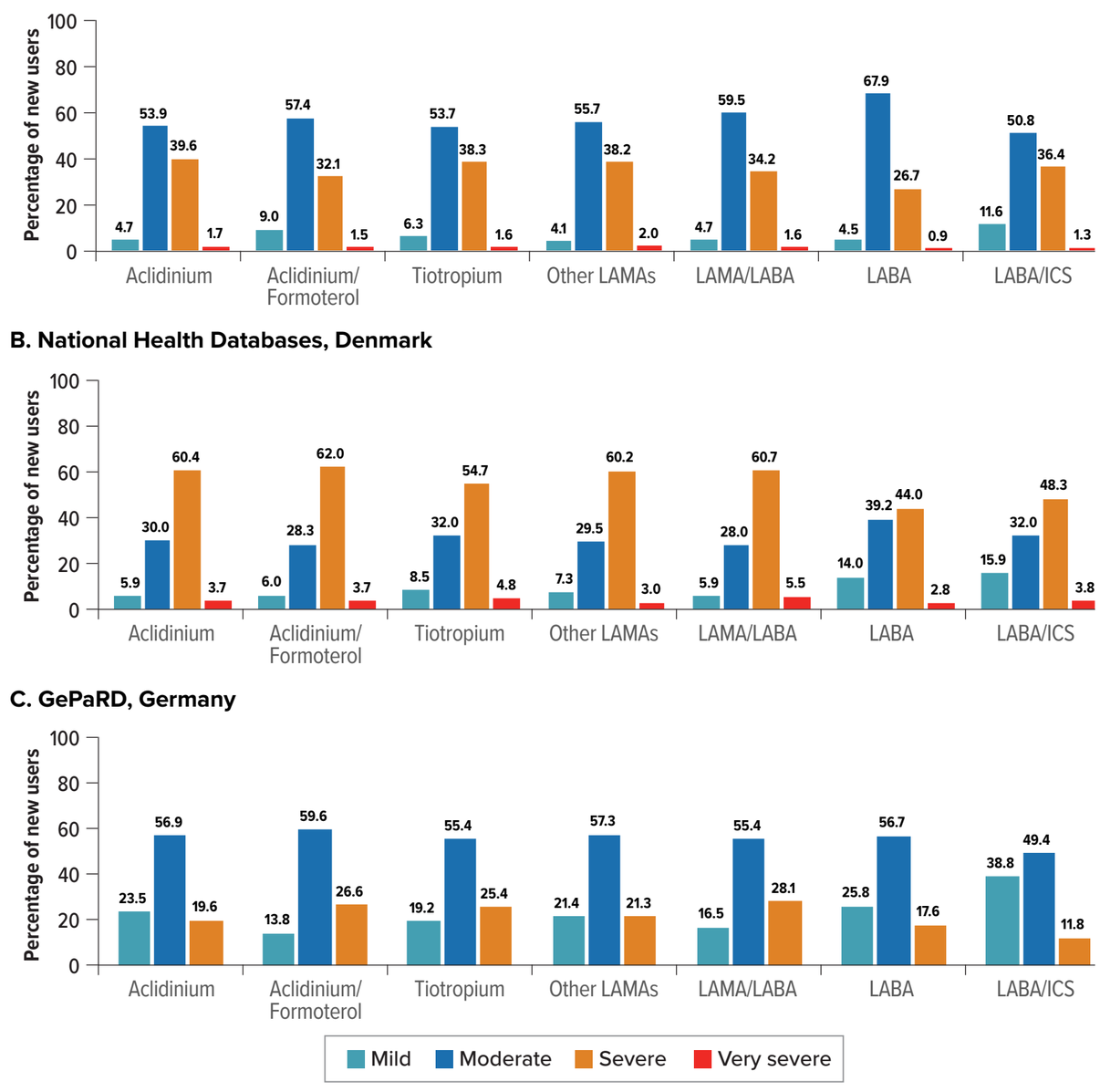

Figure 2. Distribution of New Users of Aclidinium and Aclidinium/Formoterol According to Label, by Data Source, Country

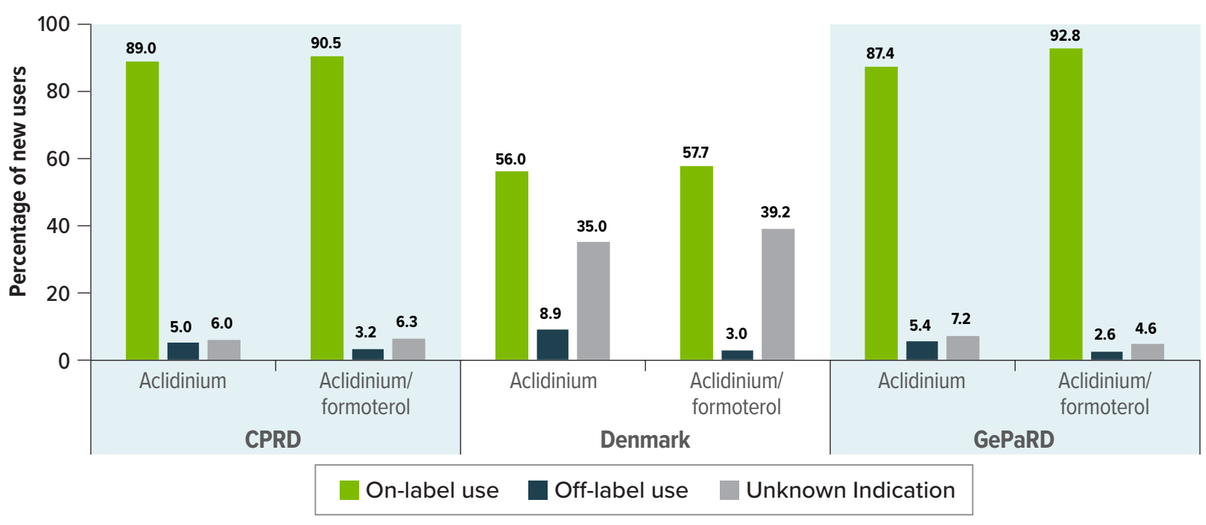

Table 3. Off-Label Prescribing and Unknown Indication Among New Users of Aclidinium and Aclidinium/Formoterol, by Data Source, Country

Evaluation of Indication	CPRD, UK		National Health Databases, Denmark		GePaRD, Germany	
	Aclidinium (N = 4,871) %	Aclidinium/ Formoterol (N = 2,153) %	Aclidinium (N = 2,836) %	Aclidinium/ Formoterol (N = 2,586) %	Aclidinium (N = 9,961) %	Aclidinium/ Formoterol (N = 10,069) %
Off-label use[a]	**5.0**	**3.2**	**8.9**	**3.0**	**5.4**	**2.6**
Children, aged < 18 years	0.0	0.0	0.2	0.0	0.1	NR
Asthma only	5.0	3.2	8.8	3.0	5.4	2.6
Unknown indication	**6.0**	**6.3**	**35.0**	**39.2**	**7.2**	**4.6**
Lung cancer[a]	0.4	0.3	0.7	0.9	0.2	0.2
Other respiratory conditions[a]	5.6	5.7	2.8	3.4	0.2	0.1
No lung cancer or other respiratory conditions	0.4	0.5	32.3	35.7	6.9	4.3

NR = not reportable (data protection).

[a] Patients could be classified in more than one category.

CONCLUSIONS

- Aclidinium and aclidinium/formoterol are prescribed mainly according to the approved indication. Off-label use was mostly related to a diagnosis of asthma without a COPD diagnosis recorded; however, it cannot be ruled out that a patient may have had childhood asthma that later resolved or evolved to asthma-COPD syndrome in adulthood. Pediatric use was anecdotical. Unknown indication in Denmark is driven by the lack of primary care diagnoses.
- Users of aclidinium, aclidinium/formoterol, and, in general, users of LAMA medications were older and had a higher prevalence of COPD, current smoking, and comorbidities than users of LABA or LABA/ICS.
- Severe and very severe COPD were more frequent in users of aclidinium, aclidinium/formoterol, and other LAMA medications than in users of LABA or LABA/ICS medications, although very severe COPD could not be evaluated in Germany. Moderate COPD was the most frequent severity category across the study medications in the UK and Germany, whereas severe COPD was the most frequent category in all study medications in Denmark. This may be partly explained by the lack of data from primary care in Denmark and different prescribing practices in these countries.

References

1. Verhamme KM, Afonso AS, van Noord C, Haag MD, Koudstaal PJ, Brusselle GG, et al. Tiotropium Handihaler and the risk of cardio- or cerebrovascular events and mortality in patients with COPD. Pulm Pharmacol Ther. 2012 Feb;25(1):19-26.

Contact Information

Elena Rivero-Ferrer, MD, MPH, FISPE
Senior Director, Epidemiology

RTI Health Solutions
Av. Diagonal, 605, 9-1
08028 Barcelona, Spain

E-mail: erivero@rti.org

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Presented at: ICPE 2020 All Access; 16-17 September 2020