



Roflumilast or Azithromycin to prevent COPD Exacerbations

# QUARTERLY CLINICAL ROUNDTABLE SERIES

RELIANCE QUARTERLY CLINICAL ROUNDTABLE SERIES

Session 1: COPD Exacerbations: Should you use long-term azithromycin or roflumilast for care in COPD patients?

SHOULD YOU USE AZITHROMYCIN?

SHOULD YOU USE ROFLUMILAST?

## January 11, 2022 | COPD Exacerbations: Should you use long-term azithromycin or roflumilast for care in COPD patients?

In the U.S., there are 750,000 hospitalizations per year for COPD exacerbations. The chance of readmissions is approximately 20% at 30 days, and 60% at 1 year. How can azithromycin or roflumilast help? In the first RELIANCE Virtual Clinical Roundtable series, hear from leading experts Dr. Richard Albert (Azithromycin) and Dr. Stephen Rennard (Roflumilast). [Slides available here.](#)

RELIANCE QUARTERLY CLINICAL ROUNDTABLE SERIES

Session 2: Preventing COPD exacerbations: Talking to patients and experts about different medicines. April 5, 2022, 12-1pm ET

EXAMPLE DISCUSSION BETWEEN A PATIENT AND HER PHYSICIAN

WHY USE AZITHROMYCIN OR ROFLUMILAST?

## April 5, 2022 | Preventing COPD exacerbations: talking to patients and experts about deciding between medicines.

How do you talk to your patients about the option between two medicines when you know they both work? Dr. Jerry Krishnan and COPD Patient Jean Rommes will roleplay a decision making process. Then we'll hear from leading experts Dr. Richard Albert and Dr. Stephen Rennard on how azithromycin or roflumilast can help.

[Slides available here.](#)

RELIANCE QUARTERLY CLINICAL ROUNDTABLE SERIES

Session 3: How to Be Successful Clinical Centers or Community Partners in RELIANCE July 26, 2022, 12-1pm ET

HEAR ABOUT REAL CHALLENGES TO RECRUITING PARTICIPANTS, WHAT'S BEEN WORKING, AND HOW TO APPLY BEST PRACTICES

## July 26, 2022 | How to be successful Clinical Centers or Community Partners in RELIANCE

Hear about real challenges to recruiting participants, what has been working, and how to apply best practices. Investigators Dr. John Veljanovski and Dr. Bushra Mina, and Community Partner Randall Harris share their experiences.

[Slides available here.](#)

RELIANCE QUARTERLY CLINICAL ROUNDTABLE SERIES

Session 4 June 13, 2023 12-1pm ET

**Journal Club: Use of roflumilast in your patient population**  
Two experts discuss use of roflumilast in specific patient populations

RoFlumilast May Increase Risk of Exacerbations When Used to Treat Poorly Controlled Asthma in People with Obesity. Dixon AE, Que LG, Kalkan R, Dransfield MT, Rogers L, Gerald LB, Kraft M, Krishnan JA, Johnson O, Hatazuchi H, Roy G, Holbrook JT, & Wise RA. Annals ATS, 2022.

Comparative Effectiveness of Roflumilast and Azithromycin for the Treatment of Chronic Obstructive Pulmonary Disease. Lam J, Torres-Miliani L, Koryon NJ, Kuhn BT. Chronic Obstr Pulm Dis. 2021.

Hosted by Jerry Krishnan, MD, PhD

Discussion moderated by Robert Wise, MD

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Have an idea for a future roundtable? Put it in the chat!



Roflumilast or Azithromycin to prevent COPD Exacerbations

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Session 4 June 13, 2023 12-1pm ET

## Journal Club: Use of roflumilast in your patient population

*Two experts discuss use of roflumilast in specific patient populations*



**Anne E. Dixon, MA, BM, BCH**  
*University of Vermont Medical Center*

**Roflumilast May Increase Risk of Exacerbations When Used to Treat Poorly Controlled Asthma in People with Obesity.** Dixon AE, Que LG, Kalhan R, Dransfield MT, Rogers L, Gerald LB, Kraft M, Krishnan JA, Johnson O, Hazucha H, Roy G, Holbrook JT, & Wise RA. *Annals ATS*, 2022.

12:10-12:25 ET



**Brooks Thomas Kuhn, MD, MAS**  
*University of California, Davis*

**Comparative Effectiveness of Roflumilast and Azithromycin for the Treatment of Chronic Obstructive Pulmonary Disease.** Lam J, Tonnu-Mihara I, Kenyon NJ, Kuhn BT. *Chronic Obstr Pulm Dis.*, 2021

.12:25-12:40 ET



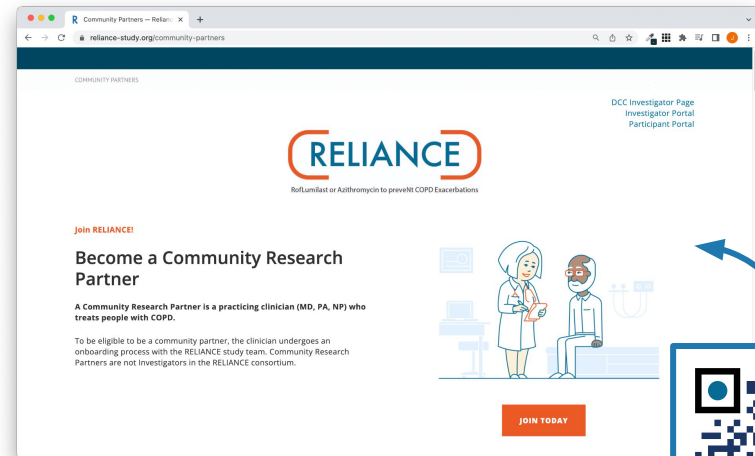
Hosted by  
**Jerry A. Krishnan, MD, PhD**  
*University of Illinois Chicago*



Discussion moderated by  
**Robert A. Wise, MD**  
*Johns Hopkins University*

1. Please mute yourself
2. Put questions + comments in the chat
3. Consider joining RELIANCE, or tell a colleague!
  - a. Long-term Azithromycin vs. Roflumilast in patients with COPD associated with chronic bronchitis
  - b. Pragmatic clinical trial embedded in clinical practice, funded by PCORI
  - c. N=470 enrolled as of June 4, 2023
  - d. ClinicalTrials.gov: NCT04069312

Want to learn more about **RELIANCE** and how to join?  
<https://www.reliance-study.org/community-partners>





## Anne E. Dixon, MA, BM, BCh

### University of Vermont

Professor of Medicine

Director, Vermont Lung Center

Chief, Division of Pulmonary and Critical Care Medicine

Attending physician, UVM Medical Center

#### **Roflumilast May Increase Risk of Exacerbations When Used to Treat Poorly Controlled Asthma in People with Obesity.**

Dixon AE, Que LG, Kalhan R, Dransfield MT, Rogers L, Gerald LB, Kraft M, Krishnan JA, Johnson O, Hazucha H, Roy G, Holbrook JT, & Wise RA. *Annals ATS*, 2022.

# Trial of Roflumilast in Asthma Management (TRiM)

Anne Dixon  
University of Vermont



# Background

- **60% of people with severe asthma are obese**
- **People with obesity often have difficult to control asthma**
- **Do not respond as well to some treatments**
- **Pressing need to develop better treatments**

# Roflumilast for treatment of asthma in obesity?

- **Studied for treatment of asthma in the past**
- **Side effect of weight loss, weight loss may improve asthma control**
  - Studies in animal models of obesity and asthma support efficacy
  - Some small case studies reporting efficacy in treatment of asthma in people with obesity

# Methods

- **Pilot to determine potential efficacy of roflumilast (500 mcg per day)**
- **Randomized, placebo-controlled, double-masked**
- **Primary outcome: change in asthma control test score**
- **24 weeks**
- **Seven Centers**

University of Vermont; University of Alabama; Northwestern University; Mount Sinai-National Jewish; Duke University; University of Illinois, Chicago; University of Arizona

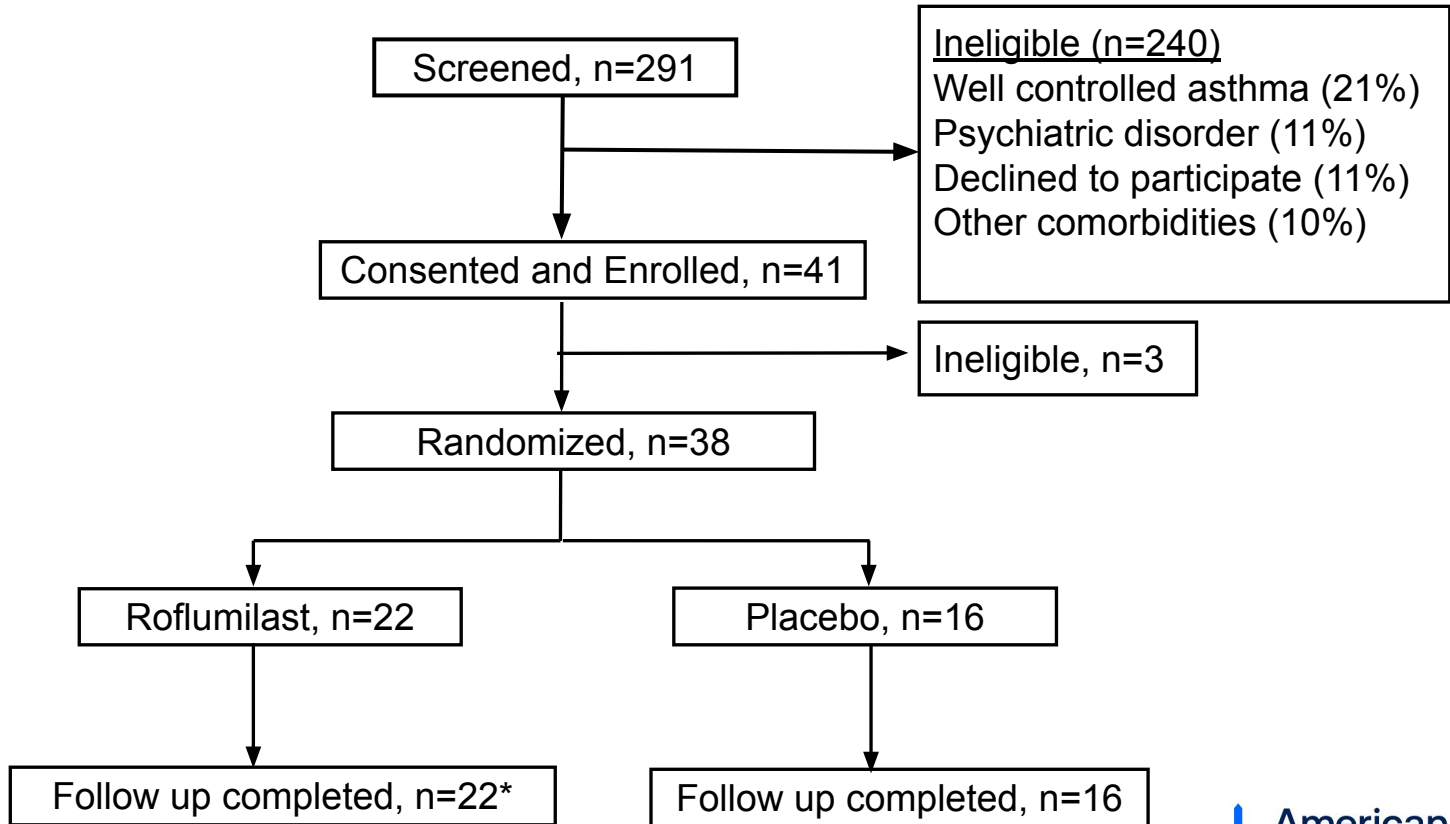


# Inclusion Criteria

- Age at least 18 years
- BMI  $\geq$  30 kg/m<sup>2</sup>
- Poorly controlled asthma (at least one)
  - ACT < 20
  - Using rescue inhaler > 2 times per week
  - Waking at night > 1 time per week
  - Asthma exacerbation in prior 6 months

# COVID-19

- Initially in person included spirometry and methacholine
- Transitioned to remote/partial in person
  - (lung function on only 17/38 participants)

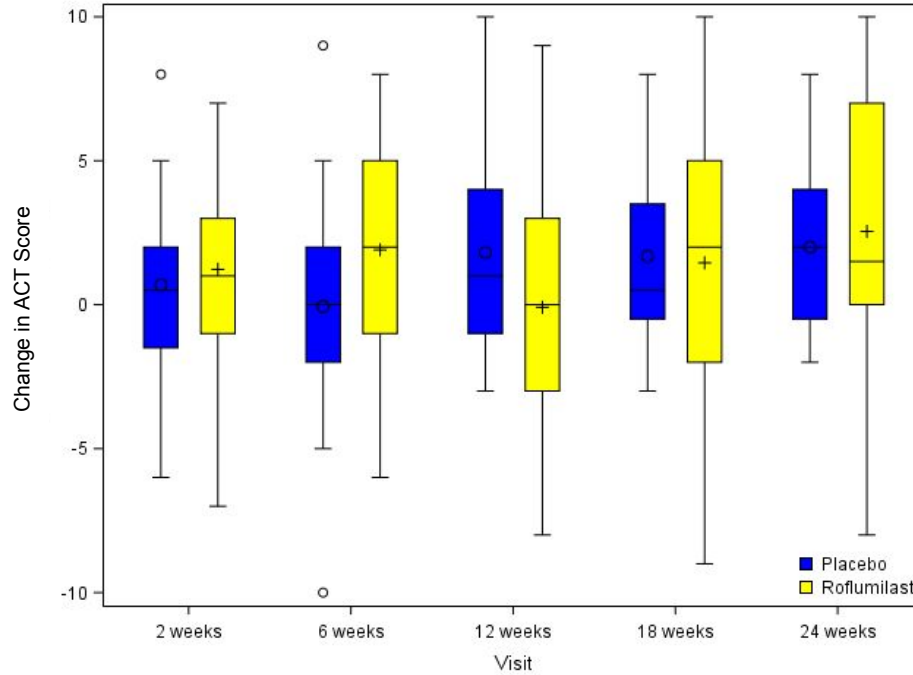


\*two stopped taking roflumilast during trial: nausea (n=1), headache (n=1)

# Baseline Characteristics

Characteristic	Placebo (N= 16)	Roflumilast (N= 22)
Age	56 (50, 63)	51 (43, 59)
BMI (kg)	36.1 (33.5, 40.1)	39.9 (35.5, 42.9)
BMI > 40	4 (25%)	10 (45%)
Male	2 (13%)	3 (14%)
Race	White	8 (50%)
	Black	6 (38%)
Hispanic Ethnicity	2 (13%)	3 (14%)
≥ 1 course of oral corticosteroids in prior year	10 (63%)	13 (59%)
ACT (range 5-25↑)	19 (16, 19)	17 (14, 18)
ASUI (range 0-1 ↑)	0.8 (0.7, 0.9)	0.7 (0.6, 0.8)
Marks AQLQ (range 1-4↓)	2.1 (1.5, 2.5)	1.8 (1.6, 2.4)

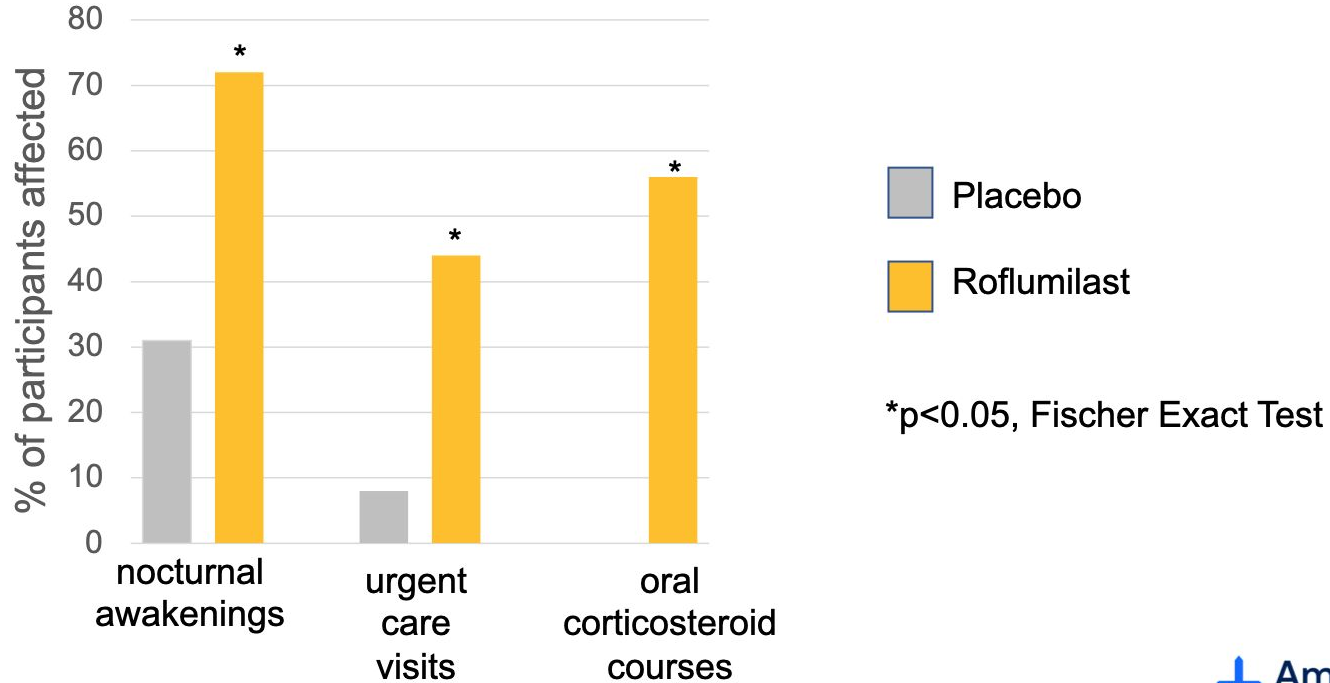
# Change in ACT score by treatment group



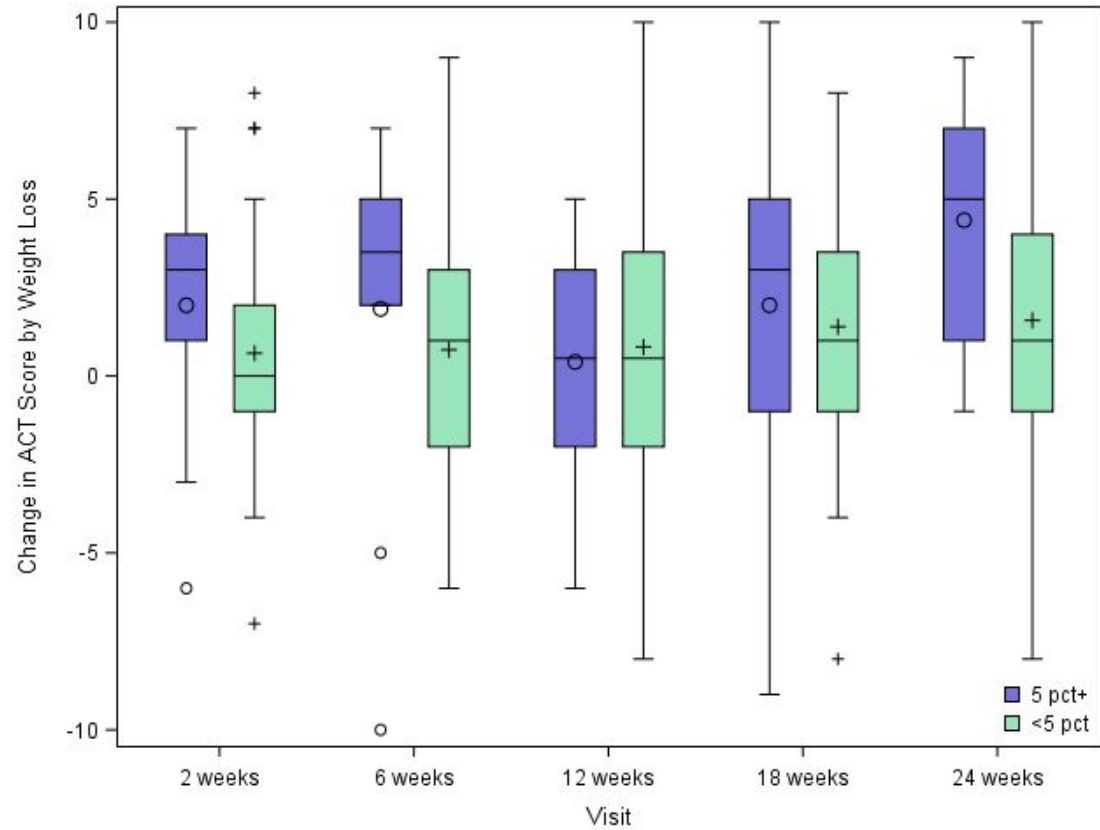
# Change in outcomes at 24 weeks

	Placebo	Roflumilast	P-value
<b>N</b>	16	22	
<b>ACT</b> (range 5-25↑)	2.0 (-0.5, 4.0)	1.5 (0.0, 7.0)	0.58
<b>ASUI</b> (range 0-1 ↑)	0.9 (0.8, 0.9)	0.9 (0.8, 0.9)	0.49
<b>Marks AQLQ</b> (range 1-4↓)	-0.3 (-0.7, 0.0)	-0.5 (-0.8,0.0)	0.65
<b>weight</b> (kg)	-1.8 (-3.8, 0.4)	-3.7 (-5.7, -0.9)	0.21
<b>≥ 5% weight loss</b>	2 (13%)	8 (38%)	0.14

# Diary cards: Symptoms and exacerbations <sup>11</sup>



# Effect of weight loss ( $\geq 5\%$ body weight)





# Summary

- Roflumilast had no effect on asthma control or quality of life
- Roflumilast treatment was associated with increased risk of episodes of poor asthma control and exacerbations
- Loss of at least 5% of body weight associated with improved asthma control

# Discussion

- Prior studies in people with asthma (> 2000 study participants) report improved lung function, and some studies report reduced exacerbations
- Prior studies in younger, less heavy people, smaller proportion of African Americans.
- Importance of phenotyping asthma and developing personalized interventions particularly for those with obesity
- Dissociation between daily symptoms and change in clinic questionnaire scores
- Interventions to promote weight loss may improve asthma control, but caution with roflumilast
- A pivotal study of roflumilast in people with obesity and poorly controlled asthma is not warranted

# Roflumilast May Increase Risk of Exacerbations When Used to Treat Poorly Controlled Asthma in People with Obesity

Anne E. Dixon<sup>1</sup>, Loretta G. Que<sup>2</sup>, Ravi Kalhan<sup>3</sup>, Mark T. Dransfield<sup>4</sup>, Linda Rogers<sup>5</sup>, Lynn B. Gerald<sup>6</sup>, Monica Kraft<sup>7</sup>, Jerry A. Krishnan<sup>8</sup>, Olivia Johnson<sup>1</sup>, Heather Hazucha<sup>9</sup>, Gem Roy<sup>9</sup>, Janet T. Holbrook<sup>9</sup>, and Robert A. Wise<sup>9,10</sup>

Annals ATS 2023: 2; 206-214

# Acknowledgment

- **Study Participants**
- **NIH and ALA**
- **Vermont:** Olivia Johnson MD, RD, Erika Gonyaw, BS, Kevin Hodgdon, Charles G. Irvin, PhD, David Kaminsky, MD
- **Johns Hopkins:** Robert Wise, MD (center director), Janet Holbrook, PhD, MPH (deputy director), Gem Roy, MD (lead coordinator), Heather Hazucha, MPH (coordinator), Robert Henderson, MS, Andrea Lears, BS, Jill Meinert, Alexis Rea, MPH, David Shade, JD, Emily Szilágyi. Former member: Ashley McCook-Veal, MS
- **University of Alabama,** Birmingham: Mark Dransfield, MD, Renita Holmes, Jennifer Trevor, MD.
- **Duke:** Loretta Que MD, Anne Mathews, MD, Catherine Foss, RN.
- **Mount Sinai-National Jewish:** Linda Rogers
- **Northwestern University:** Ravi Kalhan, MD, Sharon Rosenberg, Lewis Smith, Jenny Hixon, Vanessa Garcia
- **University of Illinois Chicago:** Jerry Krishnan, MD, Lourdes Norwick, Lauren Castro, Nina Bracken, Wendy Haase, Julie DeLisa, Renee Taylor, PhD.
- **University of Arizona:** Lynn Gerald, PhD, Monica Kraft MD, Chelsey Large. Sarah David, MPH, Ron Schunk, RT, Tara Carr, MD.



## Brooks Thomas Kuhn, MD, MAS

University of California, Davis

Co-Director, UCD Comprehensive COPD Clinic  
Associate Professor of Clinical Medicine

***Comparative Effectiveness of Roflumilast and Azithromycin for the Treatment of Chronic Obstructive Pulmonary Disease.***

Lam J, Tonnu-Mihara I, Kenyon NJ, Kuhn BT. Chronic Obstr Pulm Dis., 2021

Original Research

## Comparative Effectiveness of Roflumilast and Azithromycin for the Treatment of Chronic Obstructive Pulmonary Disease

Jenny Lam, MD, PhD<sup>1,2</sup> Ivy Tonnu-Mihara, PharmD<sup>3</sup> Nicholas J. Kenyon, MD, MAS<sup>4,5</sup> Brooks T. Kuhn, MD, MAS<sup>4,5</sup>

***RELIANCE Journal Club***  
***June 13, 2023***

# Disclosures

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- I have no pertinent disclosures pertaining to this study

# Aim

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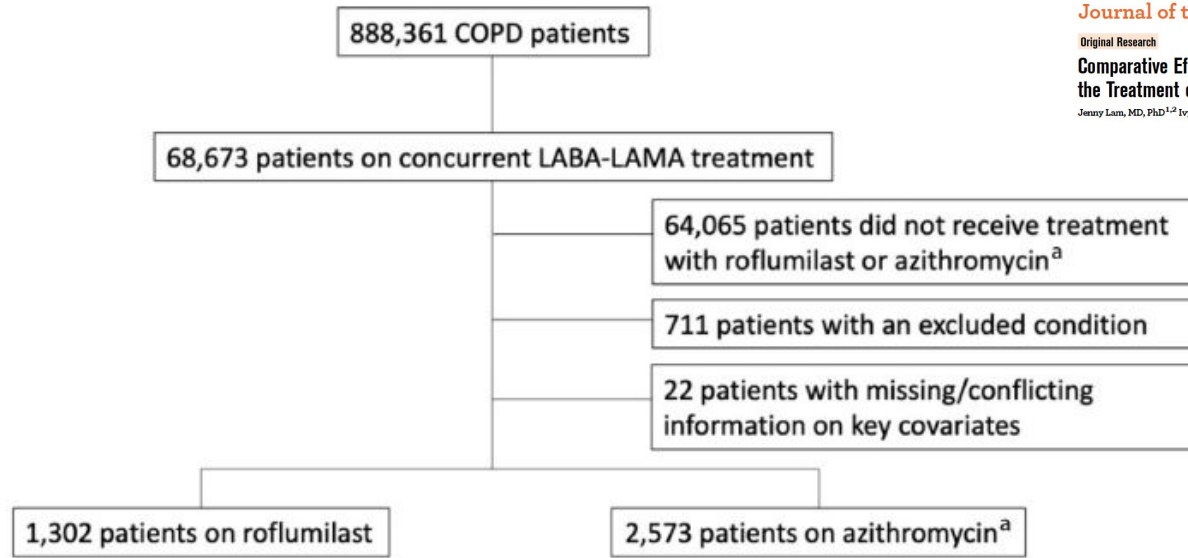
We conducted this retrospective cohort analysis using real-world data from the Veterans Health Administration (VHA) to compare the effects of roflumilast or chronic azithromycin on subsequent COPD-related hospitalization, all-cause hospitalization, and death.



# Veterans Health Administration (VHA) Data

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- VHA Corporate Data Warehouse (CDW) is a national repository of clinical and administrative data, including demographic data, inpatient and outpatient clinic visit abstracts, and prescription records
  - No spirometry or pulmonary function data
  - No reliable account for active or past tobacco use
  - No way to confirm the presence of chronic bronchitis.
  - Limited to VA health-care interactions
    - To account for hospitalizations outside of the VA, we linked the CDW data with Medicare claims
- The VHA patient population tends to be older, have more comorbidities, more tobacco abuse, and has a higher healthcare resource utilization (HCRU), including hospitalizations, than the general population
- VA systems that can affect prescribing habits
  - Cost is less of concern than formulary listing
  - Roflumilast is a non-formulary drug requiring special request



**Figure 1: Consort  
Flow Diagram**

### Inclusion:

- 1+ inpatient or 2+ outpatient visits for COPD exacerbation between 2011 to 2017
- concurrent LABA and LAMA
- prescription for either roflumilast or chronic azithromycin anytime between 2012 to 2017

### Exclusion:

- mycobacteria infections
- autoimmune or chronic inflammatory conditions
- occupational lung diseases
- bronchiectasis
- interstitial lung diseases
- Simultaneous azithro/roflumilast Rx

	Total (N = 3875)	Roflumilast (N = 1302)	Azithromycin (N = 2573)	Standardize Difference <sup>a</sup>
<b>Sociodemographic Characteristics</b>				
<b>Male, No. (%)</b>	3754 (97)	1270 (98)	2484 (97)	0.06
<b>Race, No. (%)</b>				0.08
White	3181 (82)	1038 (80)	2143 (83)	
African American	409 (11)	161 (12)	248 (10)	
Other/Unknown	285 (7)	103 (8)	182 (7)	
Hispanic	50 (1)	11 (1)	39 (2)	0.06
<b>Region, No. (%)</b>				0.14
Midwest	1007 (26)	386 (30)	621 (24)	
Northeast	493 (13)	162 (12)	331 (13)	
West	737 (19)	222 (17)	515 (20)	
South	1638 (42)	532 (41)	1106 (43)	
<b>Index Age in Years, Mean (SD)</b>	70 (7.79)	71 (7.42)	70 (7.94)	0.14
<b>History of Tobacco Use, No. (%)</b>	2742 (71)	908 (70)	1834 (71)	0.03

	Total (N = 3875)	Roflumilast (N = 1302)	Azithromycin (N = 2573)	Standardize Difference <sup>a</sup>
<b>Clinical Characteristics</b>				
<b>BMI, Mean (SD)<sup>b</sup></b>	27.26 (6.26)	27.68 (6.07)	27.05 (6.35)	0.10
<b>BMI Categories<sup>b</sup></b>				0.17
Underweight, No. (%)	234 (6)	64 (5)	170 (7)	
Normal, No. (%)	1282 (33)	380 (29)	902 (35)	
Overweight, No. (%)	1178 (31)	425 (33)	753 (30)	
Obese, No. (%)	1144 (30)	422 (33)	722 (28)	
<b>Alpha-1 Antitrypsin Deficiency, No. (%)</b>	25 (0.65)	12 (0.92)	13 (0.51)	0.05
<b>Arrhythmia, No. (%)</b>	896 (23)	293 (23)	603 (23)	0.02
<b>Asthma, No. (%)</b>	649 (17)	208 (16)	441 (17)	0.03
<b>Cancer, No. (%)</b>	556 (14)	173 (13)	383 (15)	0.05
Lung cancer, No. (%)	178 (5)	58 (4)	120 (5)	0.01
Metastatic cancer, No. (%)	50 (1)	16 (1)	34 (1)	0.01
<b>Cerebrovascular Disease, No. (%)</b>	263 (7)	87 (7)	176 (7)	0.01
<b>Chronic Kidney Disease, No. (%)</b>	391 (10)	132 (10)	259 (10)	0.00
<b>Chronic Liver Disease, No. (%)</b>	198 (5)	53 (4)	145 (6)	0.07
<b>Diabetes Mellitus, No. (%)</b>	1011 (26)	348 (27)	663 (26)	0.02
<b>Dyslipidemia, No. (%)</b>	2180 (56)	725 (56)	1455 (57)	0.02
<b>Heart Failure, No. (%)</b>	750 (19)	269 (21)	481 (19)	0.05
<b>HIV/AIDS, No. (%)</b>	22 (0.57)	5 (0.38)	17 (0.66)	0.04
<b>Hypertension, No. (%)</b>	2575 (66)	870 (67)	1705 (66)	0.01
<b>Ischemic Heart Disease, No. (%)</b>	1201 (31)	418 (32)	783 (31)	0.04
<b>Mood Disorder, No. (%)</b>	1223 (32)	348 (27)	875 (34)	0.16
<b>Obstructive Sleep Apnea, No. (%)</b>	752 (19)	273 (21)	479 (19)	0.06
<b>Osteoporosis, No. (%)</b>	246 (6)	69 (5)	177 (7)	0.07
<b>Peripheral Vascular Disease, No. (%)</b>	354 (9)	120 (9)	234 (9)	0.00



	Total (N = 3875)	Roflumilast (N = 1302)	Azithromycin (N = 2573)	Standardize Difference <sup>a</sup>
<b>SAMA, No. (%)</b>	2134 (55)	676 (52)	1458 (57)	0.10
<b>SABA, No. (%)</b>	3862 (99.7)	1298 (99.7)	2564 (99.7)	0.01
<b>ICS, No. (%)</b>	3836 (99)	1284 (99)	2552 (99)	0.05
<b>OCS, No. (%)</b>	2809 (72)	931 (72)	1878 (73)	0.03
<b>Outpatient Supplemental Oxygen, No. (%)</b>	70 (2)	21 (2)	49 (2)	0.02
<b>Treatment Characteristics</b>				
<b>Index Year, No. (%)</b>				0.48
2012	595 (15)	87 (7)	508 (20)	
2013	558 (14)	147 (11)	411 (16)	
2014	583 (15)	191 (15)	392 (15)	
2015	637 (16)	222 (17)	415 (16)	
2016	731 (19)	340 (26)	391 (15)	
2017	771 (20)	315 (24)	456 (18)	
<b>Index Season, No. (%)</b>				0.14
Spring	1085 (28)	327 (25)	758 (29)	
Summer	947 (24)	348 (27)	599 (23)	
Fall	934 (24)	343 (26)	591 (23)	
Winter	909 (23)	284 (22)	625 (24)	
<b>New Provider, No. (%)</b>	1405 (36)	432 (33)	973 (38)	0.10



**Table 3. Baseline Hospitalization Rates for Patients Who Also Have Traditional Medicare Coverage**

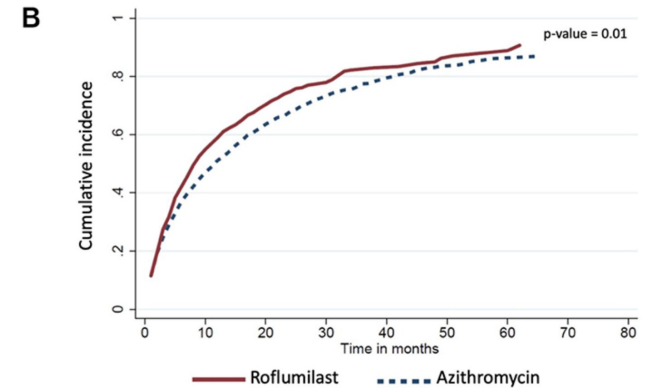
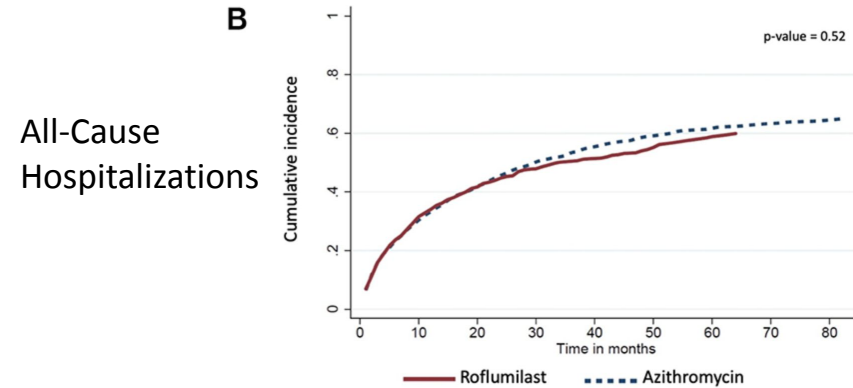
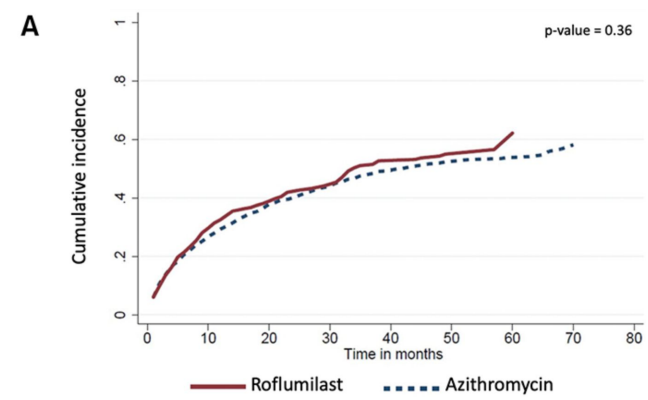
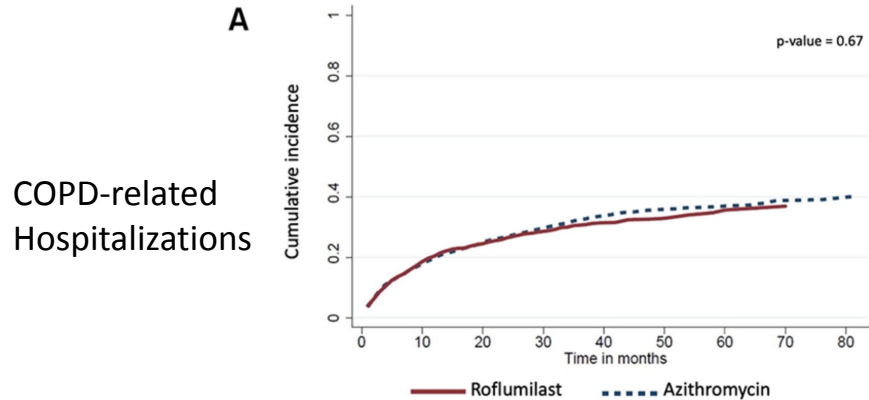
	Total (N=2030)	Roflumilast (N=659)	Azithromycin (N=1371)	Standardized Difference <sup>a</sup>
<b>All-cause</b> (per patient year), Mean (SD)				
<b>VHA Hospitalizations Only</b>	1.15 (1.93)	0.97 (1.67)	1.24 (2.04)	0.15
<b>VHA + CMS Hospitalizations</b>	1.76 (2.31)	1.67 (2.15)	1.81 (2.38)	0.06
<b>COPD-related</b> (per patient year), Mean (SD)				
<b>VHA Hospitalizations Only</b>	0.63 (1.30)	0.49 (1.01)	0.69 (1.41)	0.16
<b>VHA + CMS Hospitalizations</b>	0.88 (1.50)	0.78 (1.28)	0.93 (1.60)	0.11

<sup>a</sup>Absolute standardized differences are reported in this column.

SD=standard deviation; VHA=Veteran's Health Administration; CMS=Centers Medicare and Medicaid Services; COPD=chronic obstructive pulmonary disease.

- Cohort predominantly white, male with all-cause hospitalization rate 1.18/yr and COPD-related hospitalization 0.62/yr
- Mean BMI in the roflumilast group was 27.68, and despite the known side effect of weight loss with roflumilast, 5% of the patients were underweight at initiation
- Chronic liver disease and mood disorders both higher in prevalence in the azithromycin group.
  - FDA label for roflumilast, which recommends against use in patients with moderate-to-severe liver impairment, psychiatric events, including suicidality, and weight loss

# Cumulative Incidence of First Hospitalizations: VHA data (left) and VHA + Medicare/Medicaid events (right)



**Table 2. Effect of Roflumilast and Azithromycin on Hospitalization and Mortality**

	Hazard Ratio	P value	95% CI
<b>Main Analysis</b>			
<b>COPD-related Hospitalization</b>	1.14 <sup>a</sup>	0.05	1.00-1.29
<b>All-cause Hospitalization</b>	1.07 <sup>a</sup>	0.21	0.97-1.18
<b>Mortality</b>	1.16	0.006	1.04-1.29
<b>Sensitivity Analysis (Traditional Medicare Subgroup)</b>			
<b>COPD-related Hospitalization</b>	1.21	0.01	1.05-1.41
<b>All-cause Hospitalization</b>	1.23	0.0004	1.09-1.38
<b>Mortality</b>	1.21	0.006	1.06-1.39

- There was no significant difference in the baseline COPD-related hospitalization rate, but the azithromycin group did have a statistically significantly higher baseline all-cause hospitalization rate
- After sensitivity analysis with addition of Medicare data, roflumilast cohort found to have higher rates of hospitalization and mortality



# Conclusions

- Roflumilast was associated with death, increased COPD-related hospitalizations, and all-cause hospitalizations
- Given heterogeneity of prior roflumilast and chronic azithromycin studies and differences in study vs clinical care, difficult to directly compare the results of this study
- Prospective clinical trials are needed to directly compare the relative efficacy of these medications with similar indications: **RELIANCE study**



## Generic roflumilast is available!

1. 500 mcg tablet
2. Available online at Mark Cuban's CostPlusDrugs.com and continuing to be added at large brick and mortar chains (CVS, Walgreens, grocery stores, etc.)
3. RELIANCE is developing a resource for locating availability at [reliance-study.org/generic](https://reliance-study.org/generic) (AL,IL,KS,MS,OH already many locations)



*Point your phone camera at the QR code to go to [reliance-study.org/generic](https://reliance-study.org/generic)*





Q&A



**Robert A. Wise, MD**  
Johns Hopkins University

Questions for the speakers?

Feedback on today's  
roundtable or have a topic  
request for the next one?

*Put it in the chat!*

*Become a Community Partner:  
Complete a [brief form](#) to  
nominate yourself or a colleague  
to learn more, or point your  
phone camera at the QR code  
below.*





**Thank you!**

Join us for our next roundtable on  
Tuesday, September 19th