Pulmonary Outcomes Associated with Long-Term Azithromycin Therapy in Cystic Fibrosis

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ONLINE DATA SUPPLEMENT

Supplemental Methods

Consistent with published guidelines, pre-specified variables were selected by the investigators for propensity weighting based on the potential to impact the outcomes of interest. This was done prior to analyses and no variables were removed based on the results. Propensity scores were computed by logistic regression with 14 pre-specified variables: age group (6-11, 12-17, 18-23, 24-29,30-35,36+), maximum forced expiratory volume in one second percent predicted by GLI reference equations (FEV1pp) in the past 6 months, gender, mutation class (1-3,4/5,-), enzyme use, non-white (any non-white race and/or Hispanic ethnicity), BMI (raw over 18, percentile under 18), CF related diabetes (CFRD), liver disease, number of pulmonary exacerbations in prior 12 months (0, 1-2, 3+), calendar year at baseline, dornase alfa use, hypertonic saline use, and insurance category (Private, Medicare, Medicaid, No Insurance). An indicator of any CFTR modulator use during follow-up was added to the PS model to account for imbalance in this time-varying confounder(1).

FEV1pp matching was exact on age group and categorical maximum FEV1pp in the past 6 months (<60%, 60% to <80%, 80% to <90%, 90% to <100%, ≥100%). Caliper was set to 0.1 PS standard deviations (SD), to more closely match on variables imbalanced initially after using the default settings. This setting reduced the number of matched pairs since exposed subjects with greater than 0.1 SD difference in PS relative to any control were excluded from analysis. Marginal structural models were considered but were not used due to the nature of the exposure, which is defined over the entire period rather than treated as time varying.

In mixed effects models with random slopes, values missing after loss to follow-up were modeled by the assumption of a continued trend at the subject level. Missing values were otherwise treated as “missing at random”.

983 people with any non-tuberculous mycobacteria positive cultures were excluded. This exclusion criterion was based on culture history alone and not on a need for antibiotic treatment of this infection. Consensus treatment guidelines recommend discontinuing azithromycin in people with NTM (+) cultures unless it is included as part of a multi-drug treatment regimen. Such patients are relatively unlikely to be using chronic AZM as a CF maintenance therapy, the primary interest of our analyses. When AZM is used in this population, it is most likely to be in combination with other antibiotics to treat NTM-related pulmonary disease. For these reasons, this population presents a higher risk of misclassification and confounding that may be challenging to address in the data available, and they were excluded from our analyses.

Supplemental Tables and Figures

Table E1. Cohort 1 &2 demographics: incident chronic use of azithromycin by PA status, unmatched

	PA Positive			PA Negative		
	Control (n=834)	**AZM (n=640)**	**p**	**Control (n=2743)**	**AZM (n=498)**	**p**
Best 6mo FEV_1%, mean (sd)	81.1 (21.9)	81.7 (21.4)	0.615	94.7 (17.7)	90.0 (18.7)	<0.001
Baseline age, mean (sd)	20.3 (8.5)	18.5 (7.8)	<0.001	13.8 (6.1)	13.8 (5.4)	0.933
Any Lumacaftor/ Ivacaftor Use	59 (7.1)	34 (5.3)	0.204	159 (5.8)	24 (4.8)	0.445
PE prior 12 months			0.173			<0.001
0	479 (57.4)	339 (53.0)		2251 (82.1)	311 (62.4)	
1-2	307 (36.8)	254 (39.7)		439 (16.0)	163 (32.7)	
3+	48 (5.8)	47 (7.3)		53 (1.9)	24 (4.8)	
Male	413 (49.5)	306 (47.8)	0.55	1470 (53.6)	227 (45.6)	0.001
Non-white and/or Hispanic	128 (15.3)	90 (14.1)	0.539	427 (15.6)	70 (14.1)	0.428
Mutation class			0.064			<0.001
1-3	677 (81.2)	549 (85.8)		1814 (66.1)	396 (79.5)	
4-5	38 (4.6)	22 (3.4)		346 (12.6)	27 (5.4)	
Other	119 (14.3)	69 (10.8)		583 (21.3)	75 (15.1)	
Baseline year in 2011-2014*	443 (53.1)	270 (42.2)	<0.001	1676 (61.1)	240 (48.2)	<0.001
Dornase alfa	643 (81.3)	552 (88.9)	<0.001	2023 (78.5)	428 (88.4)	<0.001
Pancreatic enzymes	698 (83.7)	537 (83.9)	0.969	2096 (76.4)	419 (84.1)	<0.001
CF liver disease	83 (10.0)	53 (8.3)	0.314	172 (6.3)	31 (6.2)	1.000
CF related diabetes	160 (19.2)	123 (19.2)	1.000	161 (5.9)	51 (10.2)	<0.001
Hypertonic saline	358 (45.3)	306 (49.3)	0.148	1146 (44.5)	269 (55.6)	<0.001
Insurance			0.003			0.098
Private	517 (62.1)	413 (64.6)		1715 (62.8)	334 (67.5)	
Medicare	55 (6.6)	19 (3.0)		55 (2.0)	4 (0.8)	
Medicaid	214 (25.7)	184 (28.8)		807 (29.5)	131 (26.5)	
No insurance	47 (5.6)	23 (3.6)		156 (5.7)	26 (5.3)	
BMI% (<20 y/o), mean (sd)	46.3 (27.6)	47.0 (27.9)	0.730	51.0 (27.4)	47.7 (26.2)	0.020
BMI (≥20 y/o), mean (sd)	22.3 (3.6)	22.2 (3.6)	0.704	23.8 (4.8)	22.7 (4.1)	0.121

** Reference group: baseline year 2007-2010

P-values reflect chi-square hypothesis test for categorical or t-test for continuous variables.

Table E2. Cohort 3 & 4 demographics: chronic inhaled antipseudomonal TOB/AZLI, unmatched (≥ 1 year follow-up)

	INHALED TOB			INHALED AZLI		
	Low AZM (n=3122)	**High AZM (n=4868)**	**p**	**Low AZM (n=669)**	**High AZM (n=1580)**	**p**
Follow-up years, mean (sd)	2.46 (1.53)	2.68 (1.60)		2.06 (1.22)	2.29 (1.26)	
Best 6mo FEV_1%, mean (sd)	85.8 (21.8)	78.1 (23.2)	<0.001	77.2 (24.1)	71.8 (23.9)	<0.001
Baseline age, mean (sd)	17.1 (11.0)	20.7 (11.2)	<0.001	23.6 (14.0)	25.9 (13.6)	<0.001
Any Lumacaftor/ Ivacaftor Use	366 (11.7)	691 (14.2)	<0.001	92 (13.8)	260 (16.5)	0.248
PE prior 12 months			<0.001			0.021
0	1936 (62.0)	2620 (53.8)		358 (53.5)	771 (48.8)	
1-2	879 (28.2)	1632 (33.5)		238 (35.6)	619 (39.2)	
3+	133 (4.3)	356 (7.3)		44 (6.6)	143 (9.1)	
Male	1621 (51.9)	2568 (52.8)	0.482	302 (45.1)	679 (43.0)	0.368
Non-white or Hispanic	600 (19.2)	812 (16.7)	0.004	96 (14.3)	185 (11.7)	0.097
Mutation class			<0.001			0.899
1-3	2397 (76.8)	3921 (80.5)		523 (78.2)	1231 (77.9)	
4-5	157 (5.0)	242 (5.0)		46 (6.9)	103 (6.5)	
Other	568 (18.2)	705 (14.5)		100 (14.9)	246 (15.6)	
Baseline year in 2013-2016*	1392 (44.6)	1622 (33.3)	<0.001	354 (52.9)	743 (47.0)	0.012
Dornase alfa	2605 (83.4)	4226 (86.8)	<0.001	554 (82.8)	1353 (85.6)	0.101
Pancreatic enzymes	2705 (86.6)	4207 (86.4)	0.803	578 (86.4)	1397 (88.4)	0.205
CF liver disease	237 (7.6)	366 (7.5)	0.939	64 (9.6)	123 (7.8)	0.188
CF related diabetes	355 (11.4)	785 (16.1)	<0.001	135 (20.2)	368 (23.3)	0.118
Hypertonic saline	1481 (47.4)	2684 (55.1)	<0.001	384 (57.4)	982 (62.2)	0.039
Insurance			<0.001			0.033
Private	1642 (52.6)	2795 (57.4)		412 (61.6)	1028 (65.1)	
Medicare	99 (3.2)	235 (4.8)		31 (4.6)	106 (6.7)	
Medicaid	998 (32.0)	1237 (25.4)		140 (20.9)	281 (17.8)	
No insurance	167 (5.3)	269 (5.5)		48 (7.2)	104 (6.6)	
BMI% (< 20 y/o), mean (sd)	48.9 (27.7)	47.7 (27.3)	0.126	49.0 (27.3)	47.8 (26.4)	0.496
BMI (≥ 20 y/o), mean (sd)	22.7 (4.0)	22.4 (3.7)	0.056	23.1 (3.9)	23.0 (3.9)	0.834

* Reference group: baseline year 2010-2012

P-values reflect chi-square hypothesis test for categorical or t-test for continuous variables.

Table E3. FEV1 Rate of Change outcomes among cohorts 1 & 2: incident chronic use of azithromycin

Propensity Matched Cohort	**PA Positive (n=752)**	**PA Negative (n=814)**
FEV1 PP Slope/year (all data)		
Control	-2.41	-1.70
Chronic AZM	-1.53	-1.46
Chronic AZM – Controls	**0.88**	**0.24**
Standard Error for Chronic AZM – Controls	0.30	0.28
p-value	0.003	0.398
FEV1 PP Slope/year (yearly maximum)		
Control	-2.25	-1.47
Chronic AZM	-1.44	-1.24
Chronic AZM – Controls	**0.81**	**0.23**
Standard Error for Chronic AZM – Controls	0.24	0.24
p-value	0.001	0.345
Yearly FEV1 PP Estimates (yearly maximum)		
Year 0 Controls (reference)	85	96
Year 0 Chronic AZM - Controls (p-value)	0.56 (0.72)	-0.78 (0.52)
Year 1 Chronic AZM - Controls (p-value*)	0.65 (0.87)	0.06 (0.13)
Year 2 Chronic AZM - Controls (p-value*)	1.90 (0.036)	-0.15 (0.32)
Year 3 Chronic AZM - Controls (p-value*)	2.84 (0.002)	0.05 (0.27)
* Reference for p-value is Year 0 Chronic AZM – Controls		

Un-Matched Cohort	**PA Positive (n=1463)**	**PA Negative (n=3208)**
FEV1 PP Slope/year (all data)		
Control	-2.15	-1.54
Chronic AZM	-1.53	-1.27
Chronic AZM – Controls	0.62	0.27
Standard Error for Chronic AZM – Controls	0.21	0.19
p-value	0.003	0.160
FEV1 PP Slope/year (yearly maximum)		
Control	-2.14	-1.30
Chronic AZM	-1.33	-1.35
Chronic AZM – Controls	0.81	-0.049
Standard Error for Chronic AZM – Controls	0.19	0.17
p-value	<0.001	0.773

Yearly FEV1 PP Estimates (yearly maximum)		
Year 0 Controls (reference)	83	97
Year 0 Chronic AZM - Controls (p-value)	0.44 (0.706)	-4.99 (<0.001)
Year 1 Chronic AZM - Controls (p-value*)	1.70 (0.003)	-4.25 (0.063)
Year 2 Chronic AZM - Controls (p-value*)	2.21 (<0.001)	-4.78 (0.654)
Year 3 Chronic AZM - Controls (p-value*)	2.98 (<0.001)	-4.97 (0.974)

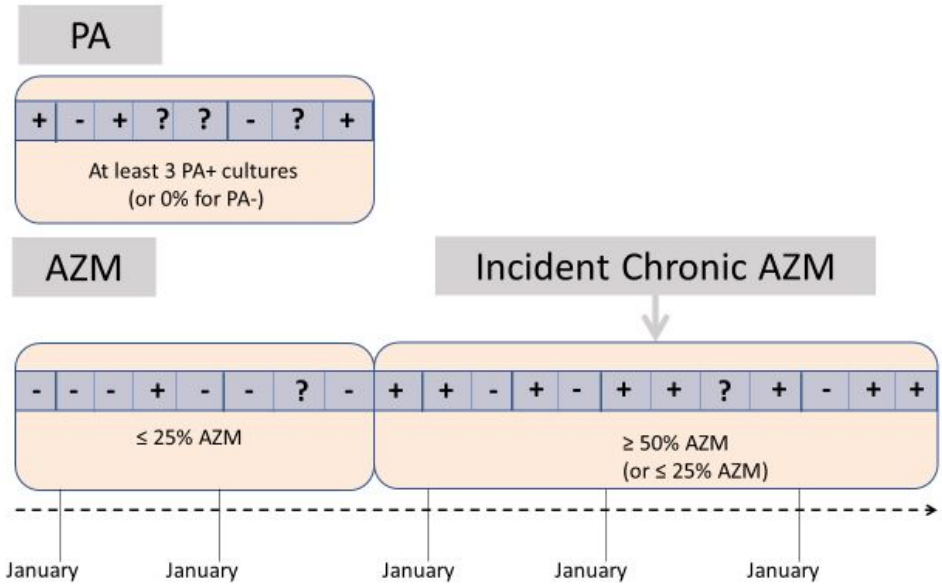
* Reference for p-value is Year 0 Chronic AZM – Controls

Table E4. FEV1 rate of change and pulmonary exacerbation (PEx) outcomes among cohorts 3 & 4: chronic inhaled antipseudomonal TOB/AZLI who were PA(+), by follow-up time.

	TOB	**AZLI**	**TOB**	**AZLI**
Follow-up time	1+ Years	1+ Years	2+ Years	2+ Years
N	1496	466	768	158
FEV1 PP Slope/year (all data)				
Low AZM	-1.84	-2.51	-1.57	-1.73
High AZM	-1.72	-1.73	-1.70	-1.52
High AZM – Low AZM	0.12	0.78	-0.13	0.21
Std Error for High AZM – Low AZM	0.24	0.40	0.27	0.48
p-value	0.608	0.050	0.635	0.663
FEV1 PP Slope/year (yearly maximum)				
Low AZM	-2.77	-3.18	-2.31	-1.73
High AZM	-2.64	-2.81	-2.53	-1.79
High AZM – Low AZM	0.14	0.36	-0.22	-0.07
Std Error for High AZM –Low AZM	0.25	0.62	0.29	0.58
p-value	0.572	0.557	0.448	0.905
IV Antibiotics Treated Pulmonary Exacerbations				
Low AZM mean PEx rate in 12 months	0.72	0.88	0.57	0.73
High AZM mean PEx rate in 12 months	0.73	0.89	0.63	0.85
Rate Ratio (RR)	1.01	1.01	1.10	1.16
RR 95% CI	(0.88, 1.18)	(0.79, 1.29)	(0.87, 1.38)	(0.74, 1.81)
p-value	0.843	0.939	0.417	0.531

Figure E1. Qualified Windows for cohort inclusion. Each square represents an age-quarter of clinic visits, registry "encounters" observed at the clinic. + indicates treatment for the corresponding therapy was indicated (or PA was detected) for at least one encounter in the quarter. (-) indicates that all encounters in the quarter were negative for the treatment (or PA). ? indicates that no encounters were observed in the quarter. For chronic inhaled antibiotics, E1b, cohorts 3 & 4 qualified windows were based on at least 2 quarters per year of tobramycin (TOB) or aztreonam lysine (AZLI), and no quarters of the other inhaled antibiotic, and either >= 75% or <= 25% azithromycin (AZM). Current illustration is for TOB cohort.

E1a.



E1b

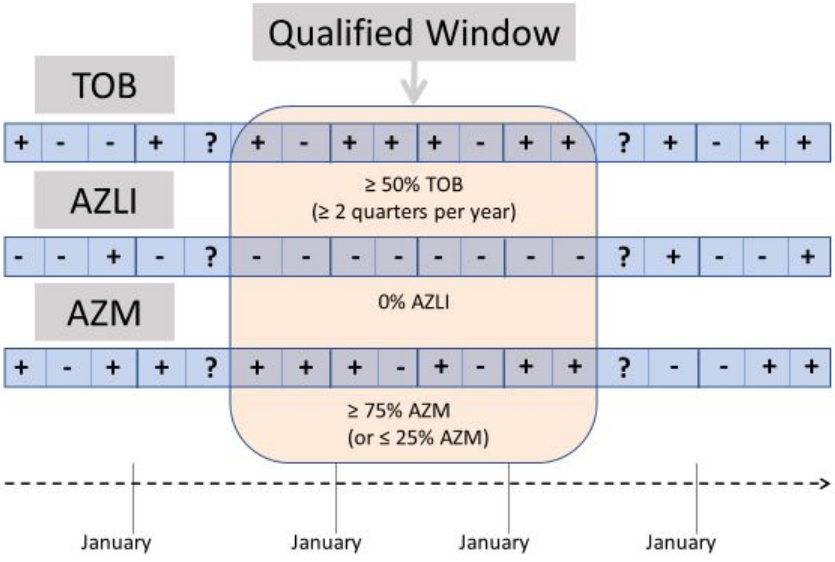
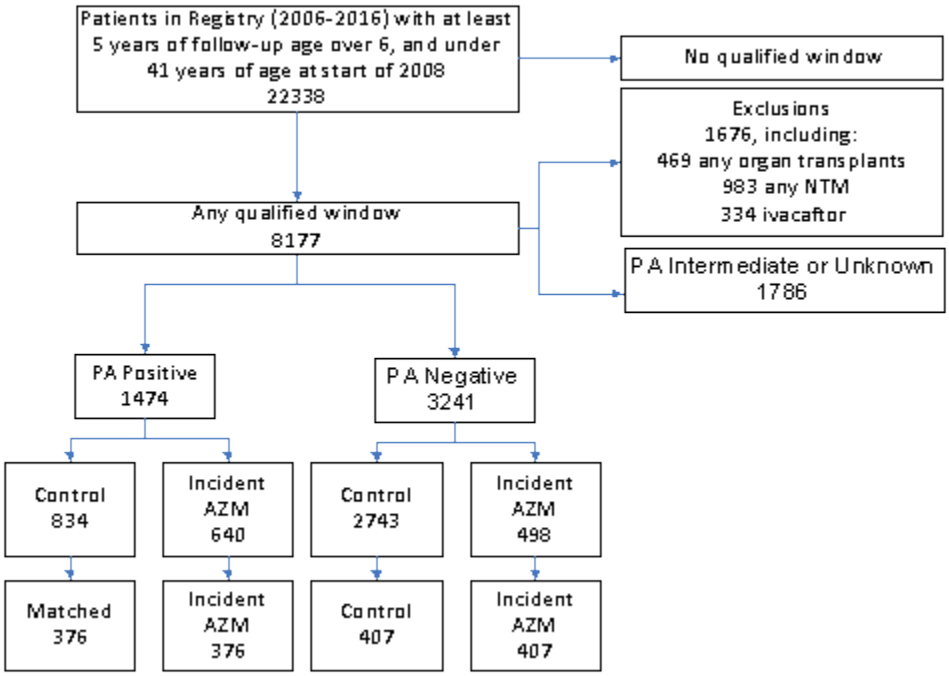


Figure E2. Subject inclusion/exclusion diagrams. E2a: cohorts 1 & 2 incident chronic AZM by PA status. E2b: cohorts 3 &4 chronic inhaled TOB/AZLI.

E2a.



E2b.

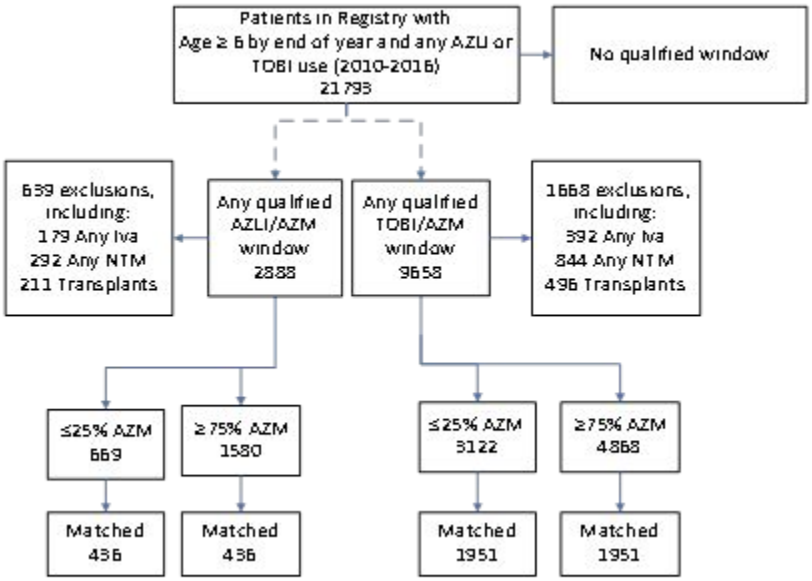
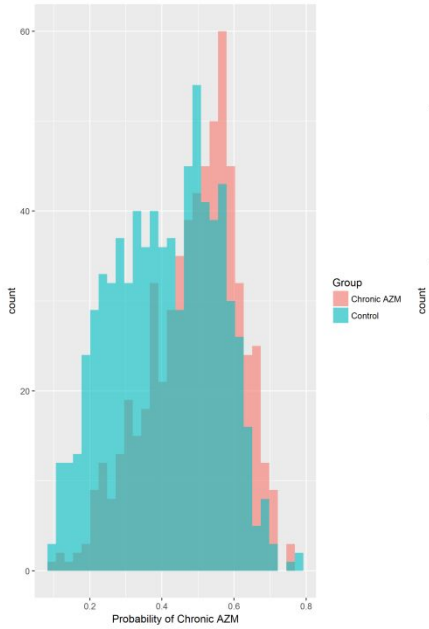


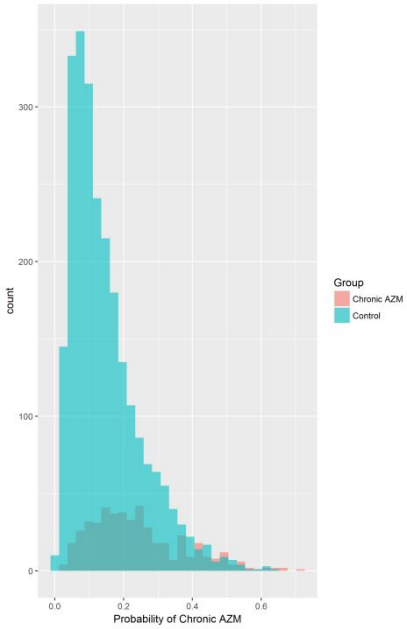
Figure E3. Propensity score distributions are summarized by counts of subjects (vertical axis) with estimated probability of AZM use from logistic regression among all subjects eligible in each cohort by AZM group (horizontal axis). The overlapping regions indicate candidates for matching due to similar "propensity" characteristics among subjects who fall in each group. Note that fewer subjects are eligible to match at the extremes for most cohorts. E3a: for cohorts 1& 2 incident chronic AZM by PA status. E3b: cohorts 3 &4 chronic inhaled TOB/AZLI.

E3a.

PA Positive

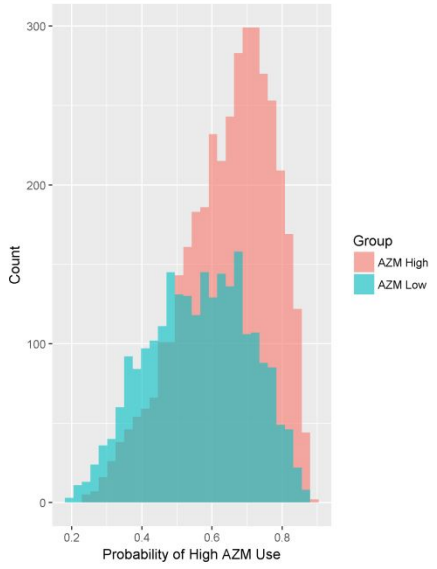


PA Negative

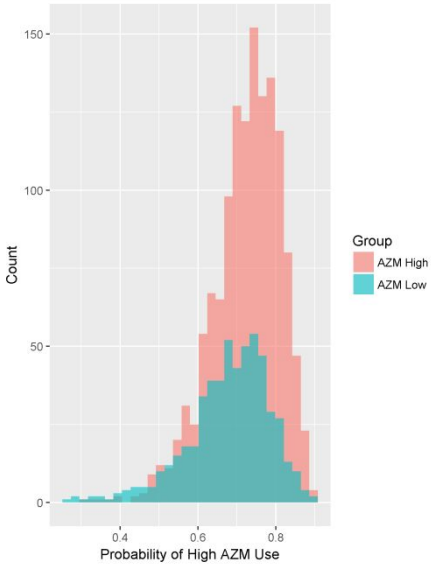


E3b.

TOB (all with 1+ years follow-up)



AZLI (all with 1+ years follow-up)



References

1. Lederer DJ, Bell SC, Branson RD, Chalmers JD, Marshall R, Maslove DM, Ost DE, Punjabi NM, Schatz M, Smyth AR, Stewart PW, Suissa S, Adjei AA, Akdis CA, Azoulay E, Bakker J, Ballas ZK, Bardin PG, Barreiro E, Bellomo R, Bernstein JA, Brusasco V, Buchman TG, Chokroverty S, Collop NA, Crapo JD, Fitzgerald DA, Hale L, Hart N, Herth FJ, Iwashyna TJ, Jenkins G, Kolb M, Marks GB, Mazzone P, Moorman JR, Murphy TM, Noah TL, Reynolds P, Riemann D, Russell RE, Sheikh A, Sotgiu G, Swenson ER, Szczesniak R, Szymusiak R, Teboul JL, Vincent JL. Control of Confounding and Reporting of Results in Causal Inference Studies: Guidance for Authors from Editors of Respiratory, Sleep, and Critical Care Journals. *Annals of the American Thoracic Society* 2018.