

SUPPLEMENTARY FILE

Title: The Impact of Exacerbation Frequency on Mortality Following Acute Exacerbations of COPD: A Registry-Based Cohort Study

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Authors: Sigrun Alba Johannesdottir Schmidt,¹ Martin Berg Johansen,¹ Morten Olsen,¹ Xiao Xu,² Joseph M. Parker,³ Nestor A. Molfino,⁴ Timothy L. Lash,^{1,5} Henrik Toft Sørensen,¹ Christian Fynbo Christiansen¹

Affiliations:

¹Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus N, Denmark

²AstraZenca LP, Gaithersburg, MD

³Medimmune LLC, Gaithersburg, MD

⁴KaloBios Pharmaceuticals, Inc., South San Francisco, CA

⁵Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA

Corresponding author: S.A.J. Schmidt. Address: Department of Clinical Epidemiology, Institute of Clinical Medicine, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark. Tel.: +45 23 69 59 47; Fax: +45 87 16 72 15. E-mail address: saj@clin.au.dk.

eTable 1: International Classification of Diseases (ICD) and Anatomical Therapeutic Chemical (ATC) Classification System codes used in the study

Codes used for identifying COPD and AECOPD

Simple and mucopurulent chronic bronchitis	ICD-10: J41
Chronic bronchitis	ICD-10: J42
Emphysema	ICD-10: J43
COPD	ICD-10: J44
Respiratory failure	ICD-10: J96.0 or J96.9
Acute respiratory infection	ICD-10: J00, J06, J10.1, J10.8, J11.1, J11.8, J20, J21, J22, B97.4
AECOPD	ICD-10: J44.1
Redeeming a glucocorticoid prescription and an antibiotic prescription on the same day	ATC codes: H02AB06/H02AB07 + J01

Comorbidities

Myocardial infarction	ICD-10: I21, I22, I23
Congestive heart failure	ICD-10: I50, I11.0, I13.0, I13.2
Peripheral vascular disease	ICD-10: I70, I71, I72, I73, I74, I77
Cerebrovascular disease	ICD-10: I60-I69, G45, G46
Peptic ulcer disease	ICD-10: K22.1, K25-K28
Liver disease	ICD-10: B15.0, B16.0, B16.2, B18, B19.0, K70.0-K70.9, K71- K74, K76.0, K76.6, I85
Diabetes	ICD-10: E10.0-E10.9, E11.0-E11.9
Moderate to severe renal disease	ICD-10: I2, I13, N00-N05, N07, N11, N14, N17-N19, Q61
Any malignancy (except lung cancer)	ICD-10: C00-C96 excl. C34
Alcoholism-related diseases	ICD-10: F10.7-F10.9, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0
Atrial fibrillation/flutter	ICD-10: I48
Medically diagnosed obesity	ICD-10: E66

Lung cancer	ICD-10: C34
Asthma	ICD-10: J45
Hypertension	ICD-10: I10-I13
Osteoporosis	ICD-10: M80, M81
Rheumatoid arthritis	ICD-10: M05
Depression	ICD-10: F32-F33
Venous thromboembolism	ICD-10: I80.1-3; I26.0; I26.9
Obstructive sleep apnea	ICD-10: G47.32

Treatment modalities

Systemic steroids	ATC codes: H02AB06 or H02AB07
Theophylline	ATC: R03DA
Antibiotics	ATC: J01
Antivirals	ATC: J05
Oxygen treatment	Treatment code: BGXA5
Lung volume reduction surgery	NOMESCO Classification of Surgical Procedures: KGDB30
COPD treatment in 12 months prior to study start*	ATC code and time-frame
Short-acting bronchodilators (beta ₂ -agonists and/or short-acting muscarinic antagonists)	Redeemed within 12 months before study start: R03AC02-10, R03AC15-17, R03BB01, R03BB02, and/or R03AK03-04
Long-acting bronchodilators (beta ₂ -agonists or long-acting muscarinic antagonists)	Redeemed within 12 months before study start: R03AC (excluding R03AC02-10 and R03AC15-17) or R03BB04-06
Double therapy with any possible combination of long-acting beta ₂ -agonists, inhaled corticosteroids, and/or long-acting muscarinic antagonists	Redeemed within 12 months before study start and within 30 days of each other: R03AC (excluding R03AC02-10 and R03AC15-17) and R03BA or Redeemed within 12 months before study start: R03AK06-07 or Redeemed within 12 months before study start and within 30 days of each other: R03AC (excluding R03AC02-10 and R03AC15-17) and R03BB04-06 or

Triple therapy with long-acting beta₂-agonists, inhaled corticosteroids, and long-acting muscarinic antagonists

Redeemed within 12 months before study start and within 30 days of each other: R03AK06-07 and R03BB04-06

Redeemed within 12 months before study start and within 30 days of each other: R03AC (excluding R03AC02-10 and R03AC15-17) and R03BA and R03BB04-06

or

Redeemed within 12 months before study start and within 30 days of each other: R03BB04-06 and R03AK06-07

Non-treated/unclassified

Remaining patients

COPD: chronic obstructive pulmonary disease; AECOPD: acute exacerbation of COPD

*Groups are mutually exclusive.

eTable 2: Adjusted hazard ratios* and 95% confidence intervals following AECOPD, northern Denmark, 2005-2009

			Frequency of AECOPD in the 12 months prior to an AECOPD			
			1	2	3+	
0 to 30 days	Overall		0.97 (0.80, 1.18)	0.90 (0.70, 1.15)	1.03 (0.81, 1.32)	
	Age	40–49	–	–	–	
		50–59	1.74 (0.85, 3.59)	0.60 (0.17, 2.13)	2.89 (1.31, 6.36)	
		60–69	1.00 (0.67, 1.50)	0.68 (0.39, 1.18)	1.10 (0.69, 1.77)	
		70–79	0.98 (0.73, 1.30)	1.05 (0.73, 1.50)	1.10 (0.75, 1.60)	
		80–89	0.70 (0.45, 1.08)	0.96 (0.56, 1.66)	0.61 (0.28, 1.34)	
		90+	–	–	–	
	Sex	Female	0.88 (0.67, 1.15)	0.90 (0.64, 1.26)	0.96 (0.67, 1.37)	
		Male	1.06 (0.80, 1.39)	0.91 (0.63, 1.31)	1.14 (0.80, 1.62)	
		Oxygen therapy within 12 months before study start	Yes	0.79 (0.27, 2.28)	0.24 (0.02, 2.45)	3.14 (0.27, 36.9)
			No	1.00 (0.82, 1.21)	0.96 (0.74, 1.23)	1.04 (0.81, 1.34)
		Baseline treatment	Non-treated/unclassified	1.60 (0.63, 4.04)	1.07 (0.11, 10.0)	2.62 (0.40, 17.3)
			Short-acting bronchodilators	1.12 (0.73, 1.73)	0.70 (0.36, 1.37)	1.38 (0.78, 2.44)
			Long-acting bronchodilator	0.69 (0.41, 1.17)	1.23 (0.67, 2.25)	0.93 (0.44, 2.00)
			Double therapy	1.01 (0.71, 1.45)	0.87 (0.54, 1.42)	1.24 (0.81, 1.91)
		Triple therapy	1.05 (0.73, 1.50)	1.10 (0.71, 1.68)	0.90 (0.56, 1.43)	
31 to 365 days	Overall		1.47 (1.30, 1.66)	1.89 (1.59, 2.25)	1.59 (1.23, 2.05)	
	Age	40–49	0.69 (0.15, 3.27)	0.79 (0.08, 7.86)	1.68 (0.19, 14.6)	
		50–59	2.13 (1.34, 3.41)	2.14 (1.07, 4.26)	3.43 (1.64, 7.15)	
		60–69	1.28 (0.98, 1.67)	1.92 (1.37, 2.69)	1.16 (0.67, 2.01)	
		70–79	1.62 (1.36, 1.94)	2.07 (1.61, 2.67)	1.56 (1.06, 2.29)	
		80–89	1.35 (1.03, 1.77)	1.66 (1.05, 2.60)	2.12 (1.15, 3.93)	
		90+	0.78 (0.19, 3.09)	8.42 (0.48, 147)	–	
	Sex	Female	1.48 (1.24, 1.75)	2.02 (1.59, 2.55)	1.65 (1.15, 2.38)	
		Male	1.47 (1.24, 1.76)	1.72 (1.32, 2.24)	1.48 (1.02, 2.14)	

		Frequency of AECOPD in the 12 months prior to an AECOPD		
		1	2	3+
Oxygen therapy within 12 months before study start	Yes	3.61 (1.80, 7.27)	4.87 (1.79, 13.2)	4.22 (0.82, 21.7)
	No	1.44 (1.27, 1.63)	1.87 (1.56, 2.24)	1.57 (1.21, 2.04)
Baseline treatment	Non-treated/unclassified	1.39 (0.75, 2.58)	3.24 (1.11, 9.46)	–
	Short-acting bronchodilators	1.30 (0.97, 1.74)	2.42 (1.65, 3.55)	1.96 (1.06, 3.62)
	Long-acting bronchodilator	1.77 (1.32, 2.38)	2.34 (1.50, 3.66)	1.00 (0.40, 2.49)
	Double therapy	1.32 (1.05, 1.65)	1.73 (1.26, 2.37)	1.76 (1.16, 2.66)
	Triple therapy	1.62 (1.29, 2.02)	1.52 (1.09, 2.13)	1.48 (0.95, 2.32)

COPD: chronic obstructive pulmonary disease; AECOPD acute exacerbation of COPD; See the text and Appendix for definitions of AECOPD frequency and GOLD treatment groups. Reference is COPD patients with no AECOPD.

*Adjusted for age (as a continuous variable), sex, and comorbidities.

Due to sparse data, we were unable to perform this analysis for some of the subgroups listed and for previous lung volume reduction surgery

eTable 3: Adjusted hazard ratios and 95% confidence intervals following severe AECOPD, northern Denmark, 2005-2009, only severe (hospitalised) AECOPDs included

			Frequency of severe AECOPD in the 12 months prior to a severe AECOPD			
			1	2	3+	
0 to 30 days	Overall		1.07 (0.85, 1.33)	1.29 (0.96, 1.75)	1.09 (0.75, 1.59)	
	Age	40–49	–	–	–	
		50–59	2.99 (1.27, 7.07)	2.87 (0.94, 8.79)	7.28 (2.44, 21.7)	
		60–69	0.94 (0.58, 1.52)	0.88 (0.47, 1.67)	0.94 (0.45, 1.93)	
		70–79	1.09 (0.78, 1.50)	1.54 (0.99, 2.39)	0.76 (0.39, 1.48)	
		80–89	0.89 (0.51, 1.57)	1.41 (0.64, 3.14)	1.42 (0.38, 5.29)	
		90+	–	–	–	
	Sex	Female	0.96 (0.70, 1.32)	1.13 (0.72, 1.77)	1.20 (0.69, 2.09)	
		Male	1.20 (0.87, 1.66)	1.53 (1.01, 2.33)	1.28 (0.75, 2.19)	
		Oxygen therapy within 12 months before study start	Yes	1.31 (0.19, 9.02)	0.93 (0.04, 24.1)	11.6 (0.23, 571)
			No	1.08 (0.86, 1.36)	1.33 (0.98, 1.80)	1.09 (0.74, 1.60)
		Baseline treatment	Non-treated/unclassified	3.10 (0.38, 25.2)	–	7.72 (0.44, 137)
			Short-acting bronchodilators	1.57 (0.93, 2.67)	1.40 (0.63, 3.12)	2.66 (0.85, 8.39)
			Long-acting bronchodilator	0.98 (0.54, 1.79)	0.77 (0.31, 1.92)	0.67 (0.22, 2.04)
		Double therapy	1.37 (0.90, 2.10)	1.44 (0.81, 2.56)	1.78 (0.94, 3.38)	
		Triple therapy	0.96 (0.62, 1.50)	2.13 (1.29, 3.53)	1.02 (0.51, 2.04)	
31 to 365 days	Overall		1.75 (1.49, 2.06)	1.67 (1.26, 2.23)	1.77 (1.15, 2.72)	
	Age	40–49	–	–	–	
		50–59	2.04 (1.13, 3.66)	3.19 (1.31, 7.78)	2.25 (0.53, 9.62)	
		60–69	1.91 (1.37, 2.66)	1.80 (1.08, 2.99)	1.85 (0.87, 3.94)	
		70–79	2.01 (1.59, 2.53)	1.65 (1.07, 2.56)	1.50 (0.76, 2.95)	
		80–89	1.06 (0.70, 1.60)	0.90 (0.33, 2.46)	2.48 (0.60, 10.3)	
		90+	–	–	–	
	Sex	Female	1.62 (1.29, 2.03)	1.96 (1.37, 2.82)	2.28 (1.29, 4.04)	
		Male	1.93 (1.53, 2.43)	1.30 (0.80-2.10)	1.28 (0.65-2.52)	
		Oxygen therapy within 12 months before study start	Yes	3.30 (1.16, 9.38)	1.50 (0.15-14.9)	–

		Frequency of severe AECOPD in the 12 months prior to a severe AECOPD		
		1	2	3+
Baseline treatment	No	1.75 (1.48, 2.06)	1.70 (1.27-2.27)	1.82 (1.18-2.80)
	Non-treated/unclassified	0.58 (0.10, 3.27)	2.49 (0.27-22.7)	0.65 (0.00-295)
	Short-acting bronchodilators	1.56 (1.06, 2.30)	1.66 (0.73-3.81)	1.08 (0.15-8.02)
	Long-acting bronchodilator	2.03 (1.39, 2.98)	1.88 (0.97-3.63)	0.75 (0.18-3.20)
	Double therapy	1.80 (1.34, 2.40)	1.81 (1.09-3.01)	2.63 (1.33-5.21)
	Triple therapy	1.90 (1.42, 2.56)	1.53 (0.91-2.57)	2.21 (1.14-4.29)

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*Adjusted for age (as a continuous variable), sex, and comorbidities.

Due to sparse data, we were unable to perform this analysis for some of the subgroups listed and for previous lung volume reduction surgery