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Risk of All-cause Mortality During and After Severe Exacerbations in Patients With Chronic Obstructive Pulmonary Disease (COPD): Post Hoc Analysis of the IMPACT Trial

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Recording by Manoj J Mammen

IMPACT TRIAL

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Objectives

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- Exacerbations of COPD are inflammatory events that result in acute worsening of respiratory symptoms, necessitating additional treatment or, in the case of severe exacerbations, hospitalization.[1]
  - Severe exacerbations are a key contributor to the clinical and economic burden of COPD and are associated with an increased risk of death.[2–4]
- The IMPACT trial demonstrated a 34% reduction in the annual rate of severe exacerbations and a 42% reduction in on-treatment ACM risk with FF/UMEC/VI versus UMEC/VI in patients with symptomatic COPD and a history of exacerbations.[5]
- This post hoc analysis investigated the risk of ACM during and following a moderate or severe exacerbation in patients enrolled in the IMPACT trial.

ACM, all-cause mortality; COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol

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Methods

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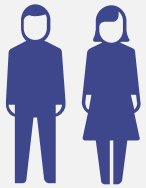
Study[1]

Randomized | Double-blind | Multicenter

Phase III

(CTT116855 [NCT02164513])

Patients[1]



- ≥40 years of age
- Symptomatic COPD: CAT score ≥10 at screening
- FEV_1 <50% predicted at screening and ≥1 moderate/severe exacerbation in prior 12 months

OR

- FEV_1 50–<80% at screening and ≥2 moderate or ≥1 severe exacerbation in prior 12 months

Treatments[1]

2 : 2 : 1 randomization
FF/UMEC/VI : FF/VI : UMEC/VI

FF/UMEC/VI	Once daily	Fluticasone furoate 100 mcg Umeclidinium 62.5 mcg Vilanterol 25 mcg
FF/VI	Once daily	Fluticasone furoate 100 mcg Vilanterol 25 mcg
UMEC/VI	Once daily	Umeclidinium 62.5 mcg Vilanterol 25 mcg

52 weeks

Post hoc analysis

Time to on-treatment ACM during, and 1–90 and 91–365 days post moderate or severe exacerbations versus baseline

- Analyzed using time-dependent repeated measures Cox model
- **Moderate exacerbation:** any exacerbation requiring antibiotics or oral/systemic corticosteroids
- **Severe exacerbation:** any exacerbation leading to hospitalization or death
- **On-treatment deaths:** actual date of death occurring up to 7 days after the last day of treatment

Cox model covariates:

- **Period**
- **Treatment group**
- **Age group**
- **Sex**
- **BMI**
- **Race**
- **Ethnicity**
- **Geographical region**
- **CV risk factors***
- **Smoking status** (Screening)
- **Exacerbation history** (≤1, ≥2 moderate/severe)
- **Post-bronchodilator % predicted FEV_1** (Screening)

*CV risk factors included past or current history of: angina pectoris; coronary artery disease; myocardial infarction; arrhythmia; congestive heart failure; hypertension; cerebrovascular accident; carotid or aorto-femoral vascular disease; diabetes mellitus; hypercholesterolemia.

ACM, all-cause mortality; BMI, body mass index; CAT, COPD assessment test; COPD, chronic obstructive pulmonary disorder; CV, cardiovascular; FEV_1, forced expiratory volume in 1 second; FF, fluticasone furoate; ITT, intent-to-treat; UMEC, umeclidinium; VI, vilanterol

1. Lipson DA, et al. N Engl J Med 2018;378:1671–80.

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Baseline characteristics and demographics (ITT population)

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	Total (N=10,355)
Age, years, mean (SD)	65.3 (8.3)
Sex (male), n (%)	6870 (66)
BMI*, mean (SD) kg/m²	26.6 (6.1)
Smoking status, n (%)	
Former smoker	6768 (65)
Current smoker	3587 (35)
Exacerbation history in prior 12 months†, n (%)	
≤1 moderate/severe exacerbations	4700 (45)
≥2 moderate/severe exacerbation	5655 (55)
Past history of pneumonia‡, n (%)	2343 (23)
CV risk factors§, n (%)	
0	3343 (32)
1	2885 (28)
≥2	4127 (40)
Post-bronchodilator FEV_1 % predicted¶, mean (SD)	45.5 (14.8)

*n=10,352; †moderate exacerbation, any exacerbation requiring antibiotics and/or oral/systemic corticosteroids, severe exacerbation, any exacerbation leading to hospitalization or death; ‡any history of pneumonia; §CV risk factors included past or current history of: angina pectoris; coronary artery disease; myocardial infarction; arrhythmia; congestive heart failure; hypertension; cerebrovascular accident; carotid or aorto-femoral vascular disease; diabetes mellitus; hypercholesterolemia; ¶n=10,347.

BMI, body mass index; CV, cardiovascular; FEV_1, forced expiratory volume in 1 second; FF, fluticasone furoate; ITT, intent-to-treat; SD, standard deviation; UMEC, umeclidinium; VI, vilanterol

1. Lipson DA, et al. N Engl J Med 2018;378:1671–80.

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Summary of adjudicated primary causes of death during and following exacerbations

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- Overall, 4401 (42.5%) patients experienced on-treatment moderate exacerbations and 1180 (11.4%) patients experienced on-treatment severe exacerbations.
- The most common cause of death was cardiovascular in the exacerbation-free period and respiratory during the exacerbation.

Periods	Causes of death, n (%)					
	Cardiovascular	Respiratory	Cancer	Unknown	Other	Total
Exacerbation-free	36 (51)	6 (9)	6 (9)	16 (23)	6 (9)	70 (100)
Moderate exacerbation						
During	1 (25)	2 (50)	0	1 (25)	0	4 (100)
1–90 days post exacerbation	9 (56)	1 (6)	1 (6)	4 (25)	1 (6)	16 (100)
91–365 days post exacerbation	2 (22)	0	3 (33)	1 (11)	3 (33)	9 (100)
Severe exacerbation						
During	1 (3)	26 (81)	0	5 (16)	0	32 (100)
1–90 days post exacerbation	1 (20)	1 (20)	0	3 (60)	0	5 (100)
91–365 days post exacerbation	2 (100)	0	0	0	0	2 (100)

Moderate exacerbation, any exacerbation requiring antibiotics and/or oral/systemic corticosteroids, severe exacerbation, any exacerbation leading to hospitalization or death. Deaths were independently adjudicated by a clinical endpoint committee to determine the primary cause of death. Percentage are presented as percent of the total number of events in each period.

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The risk of ACM significantly increased during a severe exacerbation

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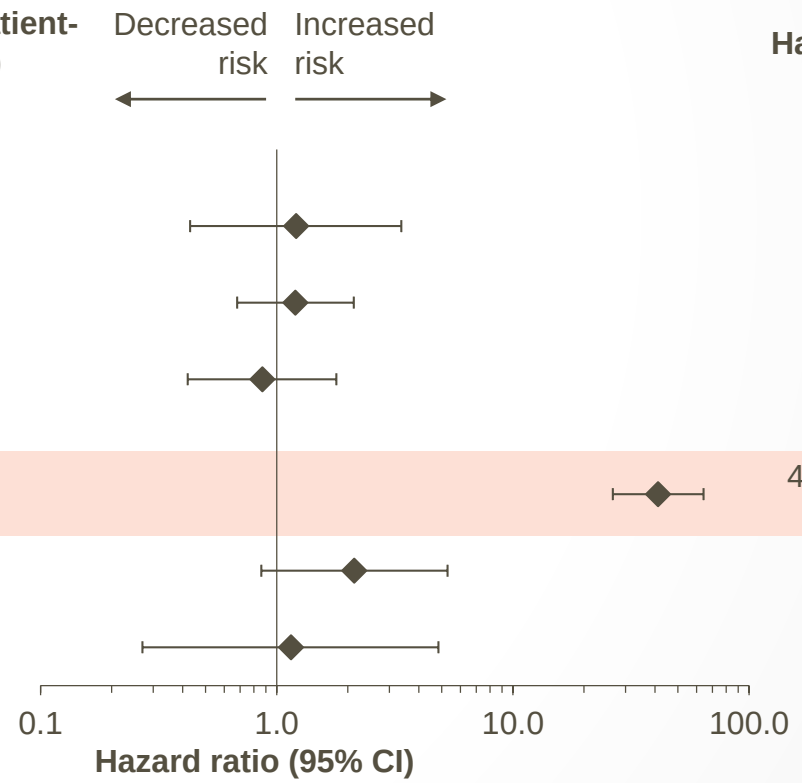
- The risk of ACM significantly increased by 41-fold during a severe exacerbation event compared with the exacerbation-free period, and decreased thereafter with neither post-exacerbation periods showing a significant difference in risk compared with the baseline period.
- As expected, there was no statistically significant increase in the risk of ACM during a moderate exacerbation.

	n*	Patients with events (ACM), n (%)†	Duration at risk (patient-years)	Event rate (per 100 patient-years)	Hazard ratio (95% CI), *P*-value
Exacerbation-free period	10,330	70 (0.7)	6280	1.11	
Moderate exacerbation					
During	4397	4 (0.1)	295	1.36	1.21 (0.43, 3.37), *P*=0.717
1–90 days post exacerbation	4201	16 (0.4)	1192	1.34	1.20 (0.68, 2.12), *P*=0.530
91–365 days post exacerbation	2805	9 (0.3)	881	1.02	0.87 (0.42, 1.79), *P*=0.707
Severe exacerbation					
During	1180	32 (2.7)	65	49.45	41.22 (26.49, 64.15), *P*<0.001
1–90 days post exacerbation	980	5 (0.5)	190	2.63	2.13 (0.86, 5.29), *P*=0.102
91–365 days post exacerbation	474	2 (0.4)	133	1.51	1.15 (0.27, 4.84), *P*=0.852



Moderate exacerbation, any exacerbation requiring antibiotics and/or oral/systemic corticosteroids, severe exacerbation, any exacerbation leading to hospitalization or death. *n is the total number of patients who spent time in each period; †percent calculated as number of patients with events divided by the total number of patients who spent time in the period.
ACM, all-cause mortality; CI, confidence interval; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol

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Conclusions

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- This time-dependent model analysis demonstrates that the risk of death was significantly increased during a severe exacerbation event in patients with symptomatic COPD and a history of exacerbations, with the risk of death decreasing following the severe exacerbation event.
  - The most common cause of death shifted from cardiovascular in the exacerbation-free period to respiratory during the exacerbation event.
- These results emphasize the importance of preventing severe exacerbations as a COPD treatment goal and the need to optimize treatment in patients at risk of exacerbations.

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COPD, chronic obstructive pulmonary disease

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CO-AUTHORS' DISCLOSURES

- TF Carr received personal fees from Aimmune, AstraZeneca, GSK, Novartis, Sanofi Genzyme, and Regeneron; grant support from NIH, Aimmune, AstraZeneca, and Novartis. GJ Criner received personal fees from Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Broncus Medical, Chiesi, CSA Medical, Eolo, Gala Therapeutics, GSK, Helios Medical, Medtronic, Merck, Mereo BioPharma, NGM Pharmaceuticals, Novartis, Nuvaira, Olympus, Philips Respironics, Pulmonx, Respivant Sciences, The Implementation Group, and Verona, and has ownership interest in HGE Technologies. MT Dransfield received personal fees from AstraZeneca, Boehringer Ingelheim, PneumRx/BTG, Quark Pharmaceuticals, and GSK; grant support from the American Lung Association, Department of Defense, Department of Veterans Affairs, and NIH; contracted clinical trial support from Boehringer Ingelheim, Novartis, AstraZeneca, Yungjin, PneumRx/BTG, Pulmonx, Boston Scientific, Gala, Nuvaira, and GSK. DMG Halpin received personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Pfizer, and Sanofi; nonfinancial support from Boehringer Ingelheim and Novartis. MK Han has received personal fees from AstraZeneca, GSK, Mylan, and Boehringer Ingelheim; research support from Novartis and Sunovion. B Hartley is a contingent worker with a Contract Research Organization working on behalf of GSK and holds shares in GSK. RG Jain, D Midwinter, and DA Lipson are employees of GSK and holds stocks/shares in GSK. V Kaul and MG Kaye have nothing to disclose. M Kraft received personal fees for consulting in asthma from AstraZeneca, Sanofi, Genentech, and Chiesi; research support from NIH, ALA, AstraZeneca, Sanofi, and Chiesi, and is co-founder of RaeSedo, LLC, a company that studies peptidomimetics for treatment of asthma. D Mapel has received research grant funding from AstraZeneca, Boehringer Ingelheim, Endo Pharmaceuticals, GSK, Sunovian, and Pfizer Pharmaceuticals; personal fees from Mylan/Theravance Biopharma. PD Scanlon has served as an investigator for clinical trials sponsored by AstraZeneca, Boehringer Ingelheim, Forest, GSK, Novartis, Pearl, and Pfizer, as well as studies funded by the National Heart, Lung and Blood Institute and the Department of Defense; he has served on scientific advisory panels for GSK and Boehringer Ingelheim. D Singh has received personal fees from GSK, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Genentech, Glenmark, Menarini, Mundipharma, Novartis, Peptinnovate, Pfizer, Pulmatrix, Theravance, and Verona; grant support from AstraZeneca, Boehringer Ingelheim, Chiesi, Glenmark, Menarini, Mundipharma, Novartis, Pfizer, Pulmatrix, Theravance, and Verona. JM Wells received personal fees from AstraZeneca, Boehringer Ingelheim, Takeda, and GSK; grant support from the NIH, and contracted research support from Bayer AG, ARCUS-Med, Vertex Pharmaceuticals, Mereo BioPharma, and Verona. R Wise has received personal fees from AstraZeneca/MedImmune, Boehringer Ingelheim, ContraFect, Pulmonx, Roche, Spiration, Sunovion, Merck, Circassia, Pneuma, Verona, Bonti, Denali, Aradigm, Mylan/Theravance, Propeller Health, AbbVie, and GSK; grant support from AstraZeneca/MedImmune, Boehringer Ingelheim, Pearl Therapeutics, GSK, and Sanofi-Aventis.