Assessment of Mortality and COPD Exacerbations in GOLD E COPD Patients in the Netherlands

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Disclosures and Acknowledgements

DISCLOSURES

EMH, YZ and **JT** are employees of Sanofi and may hold stocks and/or stock options in the company.

RHS is an employee of AESARA and paid consultant to Sanofi.

KE and **NB** are employees of PPD™ Evidera™ Real-World Data & Scientific Solutions, a part of Thermo Fisher Scientific, which was hired by Sanofi to consult on this project.

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Background

- According to the World Health Organization, COPD was the fourth leading cause of death globally, resulting in 3.5 million deaths in 2021.[1]
- The mortality rate for COPD in the Netherlands was above the European Union average rate, with an estimated 39.83 deaths per 100,000 men and 30.03 deaths per 100,000 women in 2021.[2]
- Patients with COPD generally report dyspnoea, activity limitations, cough with sputum production, and/or exacerbations.[3]
- GOLD-E COPD patients experience a higher symptom burden, with periodic exacerbations leading to sudden worsening, frequent hospital visits, and increased mortality.[4]
- There are limited data on mortality rates among individuals with mild-to-very severe COPD, especially those who are GOLD E, in the Netherlands.

1. Chronic obstructive pulmonary disease (COPD) accessed on 24 Sept 2025. 2. https://www.vzinfo.nl/copd accessed on 11 Sept 2025. 3. Safiri S, et al. *BMJ.* 2022;378. 4. Bouza et al., *Rev Esp Quimioter.* 2020; 33(1):49-67

COPD, chronic obstructive pulmonary disease; GOLD-E, Global Initiative for Chronic Obstructive Lung Disease Category E.

Objective

Objective

To estimate the incidence of mortality, MACE, and exacerbations in the overall COPD population and in those with GOLD-E COPD, in real-world settings in the Netherlands

COPD, chronic obstructive pulmonary disease; GOLD-E, Global Initiative for Chronic Obstructive Lung Disease Category E; MACE, major adverse cardiovascular events.

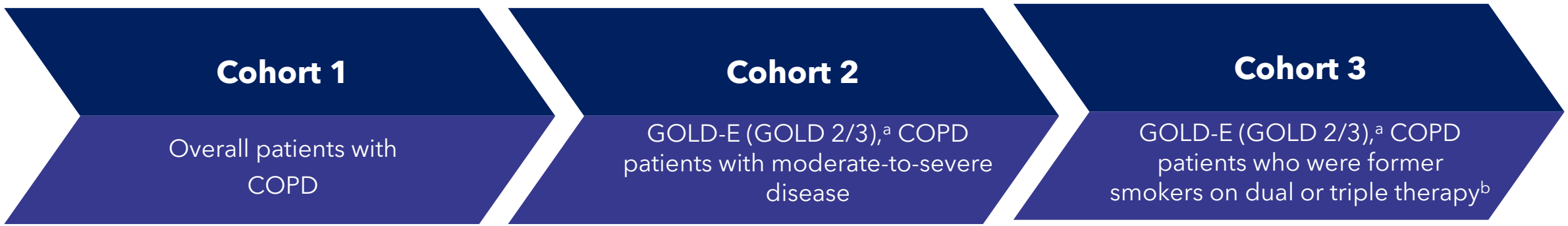
Methods

Data source and study populations

Data source:

- This study was conducted using data from the PHARMO Data Network.
- The PHARMO Data Network is a population-based electronic healthcare database in the Netherlands, following over 10 million individuals for an average of 12 years and currently covering 7+ million active persons.
- For the current study we used the general practitioner's data, hospital data and out-patient pharmacy data.

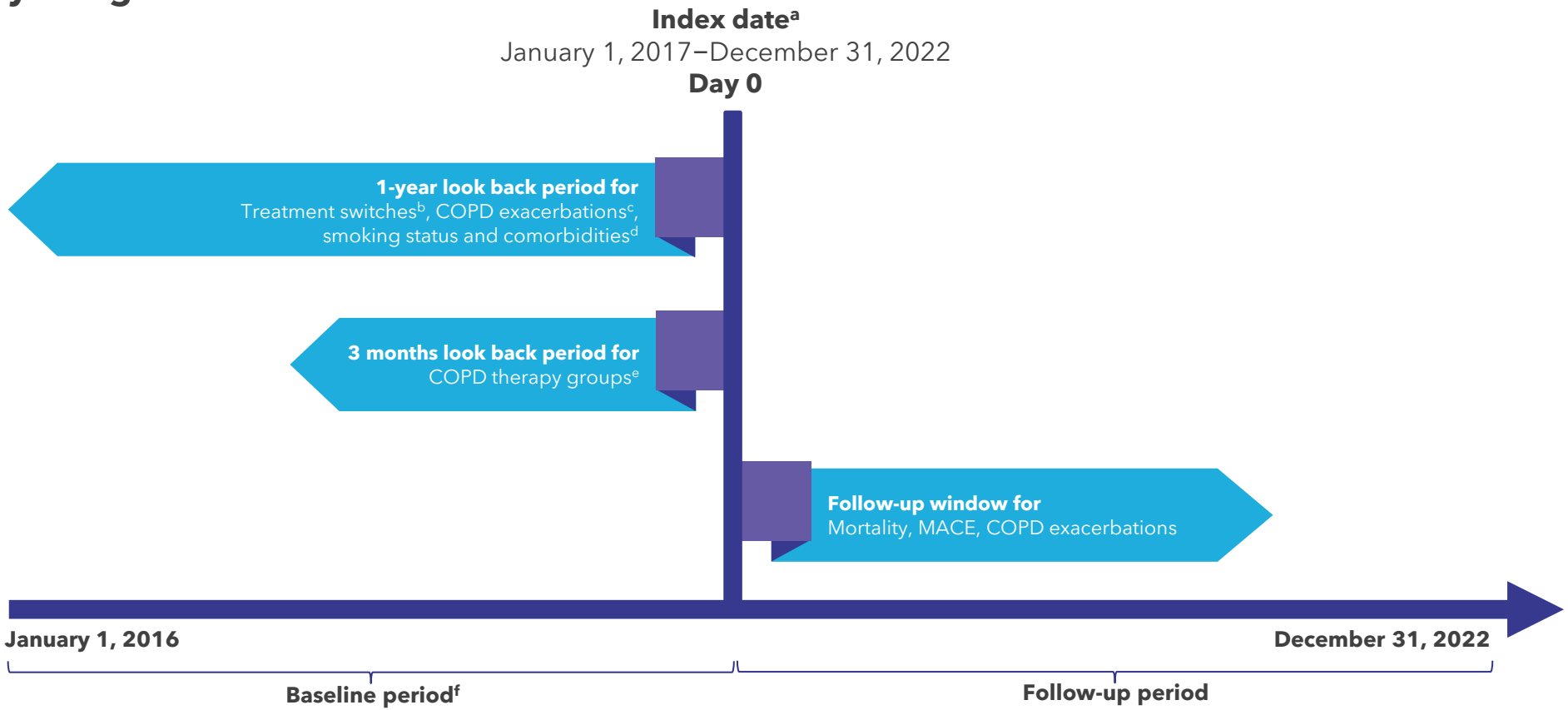
Study populations:



[a]FEV_1 value that was 30%≤FEV_1<80% (GOLD 2 or GOLD 3; the most recent record available in the previous 12 months to the index date was considered). [b]GOLD-E patients who were former smokers on dual (ICS/LABA or LABA/LAMA) or triple (ICS/LABA/LAMA) therapy.
COPD, chronic obstructive pulmonary disease; GOLD-E, Global Initiative for Chronic Obstructive Lung Disease Category E.

Study design

Figure 1. Study design



[a]The index date was defined as the earliest date when the patient was defined as having mild-to-very severe COPD, between January 1, 2017, and the end of the study period on December 31, 2022.

[b]Based on LABA, LAMA, and ICS prescriptions identified by ATC codes.

[c]Based on spirometry measures; and/or GOLD stage.

[d]Ischaemic heart disease, heart failure, stroke, heart arrythmia, bronchiectasis, osteoporosis, inflammatory bowel disease, depression, anxiety/panic attack, rheumatoid arthritis, and peptic ulcer.

[e]Monotherapy, dual therapy, or triple therapy: based on LABA, LAMA, and ICS treatments.

[f]The baseline period spanned from the date of earliest available data in the dataset to (and including) the index date. Patients were required to have ≥12 months of continuous data in all datasets.

ATC, anatomical therapeutic chemical; BMI, body mass index; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; MACE, major adverse cardiac event.

Methods

Key inclusion and exclusion criteria

Key inclusion criteria:

The patients with age ≥40 years were included in the study. The key inclusion criteria are outlined below.

Key criteria	Cohort 1 Overall patients with COPD	Cohort 2 GOLD-E (GOLD 2/3), COPD patients with moderate-to-severe disease	Cohort 3 GOLD-E (GOLD 2/3), COPD patients who were former smokers on dual or triple therapy
FEV_1	FEV_1 ≥80% (Grade 1), 50–<80% (Grade 2), 30–<50% (Grade 3), or <30% (Grade 4) during the study period	FEV_1 between ≤30% and <80% (GOLD 2 or 3)[a], based on the most recent record within 12 months prior to index date	
COPD diagnosis	≥1 encounter with COPD diagnosis (ICD-10, ICPC, or free text) on or before FEV_1 measurement	≥2 moderate exacerbations[b] (≥14 days apart) or ≥1 hospitalisation for exacerbation in the 12 months prior to index date	
Smoking status	--	--	Were former smokers
Therapy	--	--	Received dual (LABA+LAMA or ICS+LABA) or triple (LABA+LAMA+ICS) therapy within 91 days before index date

Key exclusion criteria: Diagnosed with a chronic pulmonary disease (asthma, pulmonary fibrosis, pulmonary hypertension, alpha-1 antitrypsin deficiency, or cystic fibrosis) other than COPD at any point on or before the index date. Lacking ≥12 months of continuous data before the index date in the PHARMO Data Network

[a]FEV_1 value between 30% and <80% (GOLD 2 or GOLD 3; the most recent record available in the previous 12 months to the index date was considered). [b]Moderate exacerbation was defined as a non-hospitalised COPD exacerbation or LRTI code, or ≥2 respiratory symptoms plus same-day COPD-specific antibiotics and/or oral corticosteroids prescribed for 5–14 days. Severe exacerbations were defined by hospital admission with LRTI or URTI, or an acute COPD exacerbation code (excluding pneumonia), or a primary discharge diagnosis of COPD.

COPD, chronic obstructive pulmonary disease; FEV_1 forced expiratory volume in 1 second; GOLD-E, Global Initiative for Chronic Obstructive Lung Disease Category E; ICD, International Classification of Diseases, 10th revision; ICPC, International Classification of Primary Care; ICS, inhaled corticosteroids; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection.

Methods

Study outcomes

- The cumulative incidence of mortality, MACE and COPD exacerbations was estimated from the index date until the end of follow-up across the three cohorts.

Cohort 1:
Overall patients with COPD

Cohort 2:
GOLD-E (GOLD 2/3), COPD patients with moderate-to-severe disease

Cohort 3:
GOLD-E (GOLD 2/3), COPD patients who were former smokers on dual or triple therapy

Statistical analysis

- Time-to-event analyses were conducted using KM analyses.
- The number of events, number of patients at risk, and median time to events with 95% CIs were presented.

CI, confidence interval; COPD, chronic obstructive pulmonary disease; GOLD-E, Global Initiative for Chronic Obstructive Lung Disease Category E; KM, Kaplan–Meier.

Results

GOLD-E patients were older, predominantly former smokers, and had higher rates of CV comorbidities

Table 1. Patients' sociodemographic characteristics

Variables	Cohort 1 Overall population *N* = 12,446	Cohort 2 GOLD-E (GOLD 2/3), COPD patients with moderate-to-severe disease *N* = 625	Cohort 3 GOLD-E (GOLD 2/3), COPD patients, former smokers on dual/ triple therapy *N* = 260
Sex, *n* (%)			
Male	6,841 (55.0)	340 (54.4)	160 (61.5)
Female	5,605 (45.0)	285 (45.6)	100 (38.5)
Age (years), mean (SD)	69 (9.8)	71 (9.8)	73 (9.3)
Length of follow-up (days), mean (SD)	1268 (658.3)	1269 (645.2)	1329 (637.8)
Smoking status, *n* (%)			
Current smoker	4,556 (36.6)	237 (37.9)	0 (0.0)
Former smoker	6,673 (53.6)	330 (52.8)	260 (100.0)
Non-smoker	909 (7.3)	44 (7.0)	0 (0.0)
Unknown	308 (2.5)	14 (2.2)	0 (0.0)
CV comorbidities, *n* (%)	4,887 (39.3)	287 (45.9)	122 (46.9)
Non-CV comorbidities, *n* (%)	6,078 (48.8)	337 (53.9)	133 (51.2)
Diabetes	2,370 (19.0)	146 (23.4)	69 (26.5)
Osteoarthritis	3,379 (27.1)	180 (28.8)	78 (30.0)
Osteoporosis	1,286 (10.3)	83 (13.3)	35 (13.5)
Depression	1,560 (12.5)	85 (13.6)	32 (12.3)

- ***Age:***
  GOLD-E patients were older than cohort 1, with a mean age of 71 years (SD: 9.8) in the GOLD-E moderate-to-severe cohort and 73 years (SD: 9.3) in GOLD-E with former smokers on dual or triple therapy

- ***Smoking status:***
  A large proportion of cohort 1 were former smokers (53.6%), followed by current smokers (36.6%); the smoking status in GOLD E patients (cohort 2) were similar

- ***CV comorbidities:***
  GOLD-E cohorts had higher rates of CV comorbidities (45.9%, 46.9%), and diabetes (23.4%, 26.5%), than the cohort 1 as shown in **Table 1**.

CI, confidence interval; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; GOLD-E, Global Initiative for Chronic Obstructive Lung Disease Category E; SD, standard deviation.

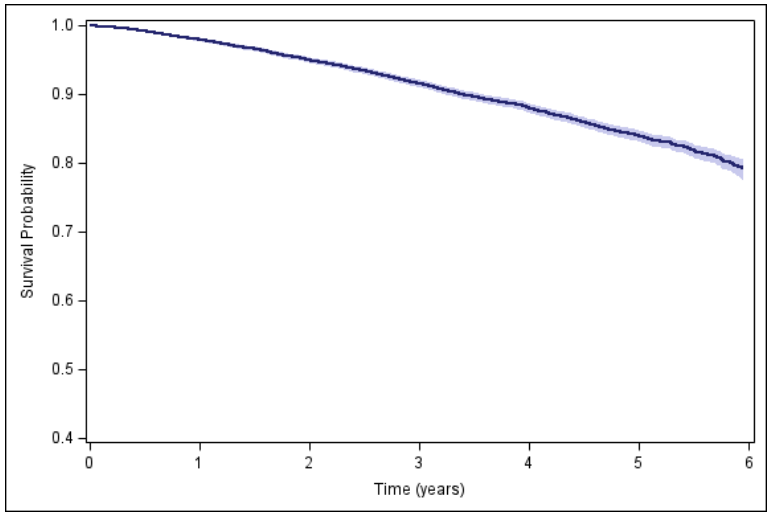
Results

Five-year cumulative all-cause mortality was higher among GOLD-E cohorts

Figure 3. All-cause mortality event at 5-year follow-up (KM estimates)[a]

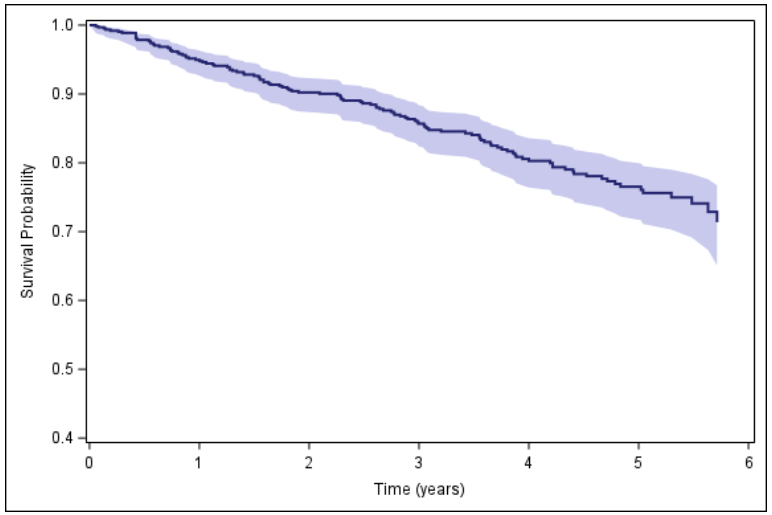
Cohort 1

The cumulative incidence of mortality at 5 years was **16.0% (95%CI: 15.2%–16.8%)**



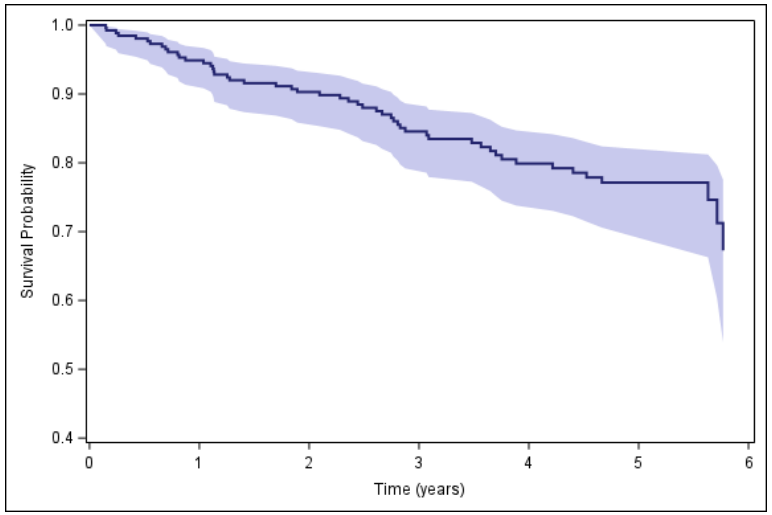
Cohort 2

The cumulative incidence of mortality at 5 years was **23.5% (95%CI: 19.7%–27.8%)**



Cohort 3

The cumulative incidence of mortality at 5 years was **22.9% (95%CI: 17.6%–29.4%)**



[a]Kaplan–Meier curve time to all-cause mortality in the mild-to-very severe COPD population
CI, confidence interval; KM, Kaplan–Meier

Results

Rate of developing a MACE, moderate exacerbations, and severe exacerbations in cohort 1

- The rate (95% confidence interval [CI]) of developing a first major adverse cardiovascular event (MACE) was 1,845 (1,717.62–1,979.88) per 100,000 person-years of follow-up (PYFU).
- The overall exacerbation rate (95% CI) was 0.33 (0.32–0.34) per PYFU, with moderate exacerbations occurring at a rate of 0.28 (0.27 –0.29) per PYFU and severe exacerbations at a rate of 0.25 (0.23 - 0.26) per PYFU.

Figure 4. Rate of developing a MACE[a], moderate exacerbation, and severe exacerbations in the overall cohort (KM curve[b])

Figure 4a. Time to first MACE in the mild-to-very severe COPD population

During the study period, the median time to MACE was not reached in the overall cohort.

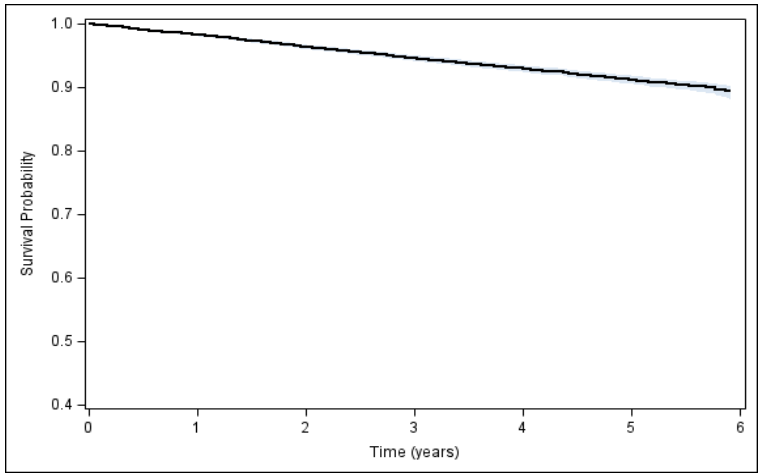


Figure 4b. Time to first moderate exacerbation in the mild-to-very severe COPD population

The median time to moderate exacerbations was 71.38 months (IQR: 18.85–NR) in the overall cohort.

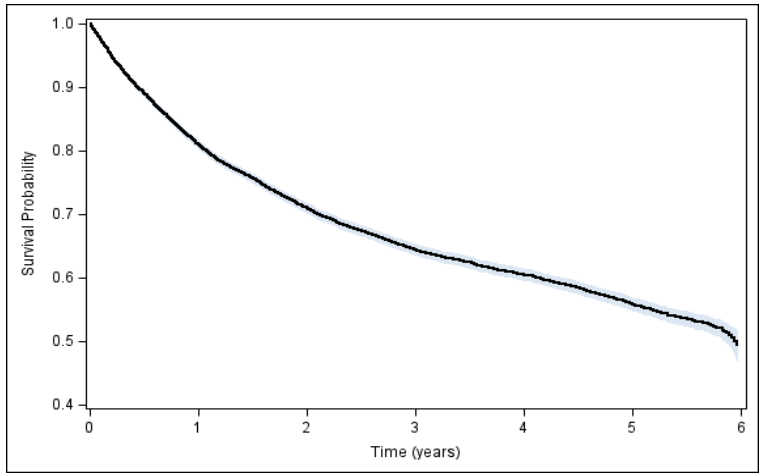
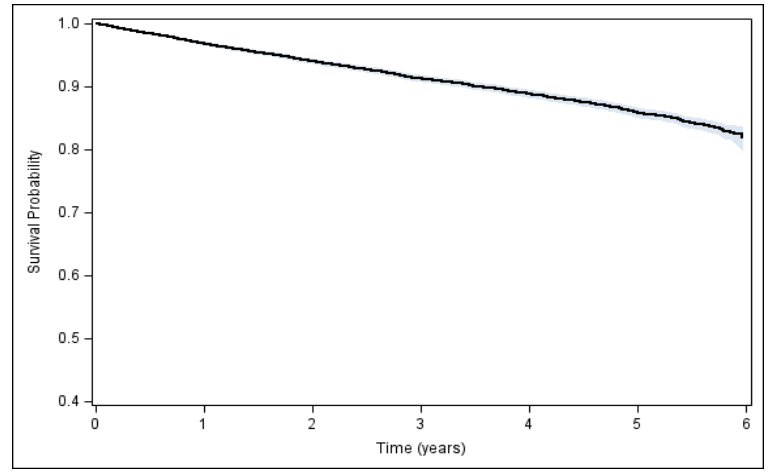


Figure 4c. Time to first severe exacerbation in the mild-to-very severe COPD population

The median time to severe exacerbations was not reached in the overall cohort during the study period.



[a]Defined as any of the following: 1. stroke (hospital admission with ICD-10 stroke code as main diagnosis), 2. myocardial infarction (hospital admission with ICD-10 MI code as main diagnosis), or 3. cardiovascular death (within 28 days of inpatient stay with primary cardiovascular diagnosis).
[b]Kaplan–Meier curve time to all-cause mortality in the mild-to-very severe COPD population
COPD, chronic obstructive pulmonary disease; PYFU, person-years of follow-up; KM, Kaplan–Meier; MACE, major adverse cardiovascular event.

Conclusion

- Our findings indicate that patients with COPD in the Netherlands had a high burden of cardiovascular comorbidities and mortality risk, especially those classified as GOLD-E.
- Among GOLD-E cohorts who were former smokers or had moderate-to-severe disease, the 5-year mortality was observed in approximately one-fourth of patients.

Limitations

- The mortality incidence was based on KM analysis, which has inherent limitations. Furthermore, there was a substantial reduction in sample size for cohorts 2 and 3, which may have affected the robustness of the findings.

COPD, chronic obstructive pulmonary disease; GOLD-E, Global Initiative for Chronic Obstructive Lung Disease Category E; KM, Kaplan–Meier