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The importance of chronic obstructive pulmonary disease exacerbation

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Mortality in patients with chronic obstructive pulmonary disorder undergoing transcatheter aortic valve replacement: The importance of chronic obstructive pulmonary disease exacerbation

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Background Severe chronic obstructive pulmonary disease (COPD) has been associated with futile outcome after transcatheter aortic valve replacement (TAVR). Data on outcomes according to COPD severity are warranted to aid identification of patients who may not benefit from TAVR. We aimed to examine the association between risk of COPD exacerbation and 1-year mortality after TAVR.

Methods Using Danish nationwide registries we identified patients undergoing first-time TAVR during 2008-2021 by COPD status. COPD severity levels were defined as low or high risk of acute exacerbation of COPD (AE-COPD) and treatment intensity levels (none or short-term, mono/dual, triple therapy, or home oxygen). Kaplan-Meier functions and adjusted Cox regression models were used to assess 1-year mortality comparing COPD severity groups with patients without COPD.

Results We identified 7,047 patients with TAVR of whom 644 had a history of COPD (low risk of AE-COPD: 439, high risk of AE-COPD: 205). The median age of the TAVR cohort was 81.4 years (IQR: 76.8-85.1) and 55.8% were males. One-year mortality for TAVR patients without COPD was 8.5% (95% CI: 7.8-9.2) and 15.4% (95% CI: 12.5-18.2) for those with COPD (adjusted HR: 1.63 [95% CI: 1.28-2.07]). Patients with low or high risk of AE-COPD had 1-year mortality of 13.1% (95% CI: 9.8-16.3) and 20.2% (95% CI: 14.6-25.8) corresponding to adjusted HRs of 1.31 (95% CI: 0.97-1.78) and 2.44 (95% CI: 1.70-3.50) compared with patients without COPD. Patients with high risk of AE-COPD and no/short term therapy or use of home oxygen represented the subgroups of patients with the highest 1-year mortality (31.6% [95% CI: 14.5-48.7] and 30.9% [95% CI: 10.3-51.6]).

Conclusion Among patients undergoing TAVR, increasing risk of exacerbation with COPD was associated with increasing 1-year mortality compared with non-COPD patients. Patients with a high risk of exacerbation with COPD not using any guideline recommended COPD medication and those using home oxygen had the highest 1-year mortality. (Am Heart J 2023;262:100–109.)

Background

Among patients with symptomatic aortic stenosis (AS) undergoing transcatheter aortic valve replacement (TAVR), chronic obstructive pulmonary disorder (COPD) is a frequent comorbidity (14-43%).[1-5] COPD is a marker of higher risk of morbidity and mortality for patients evaluated for valvular intervention.[6,7] Accordingly, patients

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Abbreviations: AE, Acute exacerbation; AS, Aortic stenosis; ATC, Anatomical therapeutic chemical classification system; CI, Confidence interval; COPD, Chronic obstructive pulmonary disease; GOLD, The global initiative for chronic obstructive lung disease; HR, Hazard ratio; ICD, International classification of diseases; ICS, Inhaled corticosteroid; IPW, Inverse probability of treatment weighting; LABA, Long-acting beta agonist; LAMA, Long-acting muscarinic antagonist; SABA, Short-acting beta agonist; SAMA, Short-acting muscarinic antagonist; SAVR, Surgical aortic valve replacement; TAVR, Transcatheter aortic valve replacement.

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with COPD are often classified as part of the high-risk surgical population among patients with symptomatic AS, in turn, these patients are more frequently treated with TAVR instead of surgical aortic valve replacement (SAVR).[1,5,8] Nevertheless, attention have emerged concerning patients with severe COPD, in which TAVR may be futile or do not provide marked symptom relief.[9]

Current evidence has associated COPD with higher mortality[4,10] and less improvement in functional class compared with those without COPD among patients undergoing TAVR. Notably, it has been suggested that TAVR is futile among the most severely affected patients with COPD.[4] COPD is a heterogenous clinical syndrome characterized by persistent respiratory symptoms and not-fully reversible air flow limitation.[11,12] Severity of the disease has been classified according to degree of airflow limitation, burden of symptoms, and risk of acute exacerbation with COPD (AE-COPD).[12] Importantly, AE-COPD is a critical event for the patient and is associated with decline in lung function, quality of life, and survival.[13,14] Unselected data on outcomes after TAVR among patients with COPD according to risk of AE-COPD are warranted to aid clinical decision making in the identification of candidates who may not benefit from TAVR.

Therefore, in a population-based cohort of patients undergoing first-time TAVR, we assessed 1-year mortality and the composite of mortality or rehospitalization according to risk of AE-COPD, as a proxy for COPD severity, using patients without COPD as reference group.

Method

Data sources

We conducted this observational cohort study using Danish nationwide registries. The Danish National Health Services provides tax-funded universal access to health care along with partial reimbursement of prescribed pharmacotherapy.[15] The unique personal identifier code, assigned to all Danish citizens at birth or upon immigration, allows accurate linkage of data at the individual level.[16] We obtained data from Danish National Patient Registry holding information on all nonpsychiatric hospital admissions since 1977 and on all hospital outpatient specialist clinic and emergency room contacts since 1995 and surgical procedures and therapies since 1996;[17] the Danish National Prescription Registry holding detailed information on all redeemed prescriptions since 1995;[18] the Danish Civil Registration System holding data on date of birth, sex, migration, marital, and vital status;[16] Statistics Denmark holding information on educational level from Danish Education Registers;[19] and the Danish Register of Causes of Death.[20] Data on causes of death were available until 31 December 2018.

Study population

We identified patients who underwent first-time TAVR between 1 January 2008 and 31 December 2021. Then, patients with a history of COPD before date of TAVR (index date) was identified as a primary in- or outpatient diagnosis code or as a secondary diagnosis code in relation to an admission with acute respiratory failure or pneumonia.[21] The positive predictive value of COPD has been reported to be high (92%-100%).[21,22] Patients aged below 40 years were excluded to minimize misclassification between asthma and COPD. The cohort was followed from index date until all-cause mortality, emigration, 1-year of follow-up, or end of study period (31 January 2022), whichever came first.

COPD severity

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) severity classification have been designed to risk stratify patients according to airflow limitation, burden of symptoms, and risk of AE-COPD to guide initiation and escalation of medical treatment.[12] As done previously, we used AE-COPD history obtained 1 year preceding index date as proxy for COPD severity.[12,23] According to the GOLD classification,[12] AE-COPD risk was classified as *low* if the patient had 0-1 out-patient AE-COPDs and 0 in-patient AE-COPD the year preceding index date. Accordingly, AE-COPD risk was classified as *high* if the patient experienced $\geq$2 out-patient AE-COPDs or $\geq$1 in-patient AE-COPD. Out-patient AE-COPD was defined as redeemed oral corticosteroid 1-year preceding index date using data from the Danish National Prescription Registry. Redemption of oral corticosteroid prescriptions had to be separated by at least 28 days between dates of dispensing to be counted as two separate episodes. Data on in-patient AE-COPD were obtained from the Danish National Patient Registry. Further, guideline-recommended COPD treatment intensity levels (eTable 1) were added as an elaboration of the COPD severity level.[24] Data on redeemed prescriptions were obtained 180 days before index date for patients with COPD (All International Classification of Diseases, 10th revision, (ICD-10) codes and Anatomical Therapeutic Chemical Classification System (ATC) codes are provided in eTable 2).

Outcomes

The primary outcome was 1-year all-cause mortality. The secondary outcome was the composite of 1-year mortality or all-cause re-hospitalization. A rehospitalization was defined as any in-patient hospitalization with at least one overnight stay.

Study covariates

Data on comorbidities were obtained in a 10-year fixed period preceding the index date using any primary or secondary in- or outpatient diagnosis codes.

The fixed period was chosen to report conditions with persistent clinical importance. The Hospital Frailty Risk Score based on ICD-10 codes was used to categorize patients into subgroups with low, intermediate, and high frailty.[25] Hemoglobin, albumin, and creatinine levels within one year prior to index date were obtained from a database covering blood samples from 4 of 5 regions in Denmark. The baseline level was defined as the most updated sample before index date. Lastly, educational level was defined as highest achieved educational level prior to index.[26] Then, we identified data on any previous procedure with percutaneous coronary intervention (PCI) and/or coronary artery bypass grafting (CABG). In-hospital events were defined as any need for intensive care, renal replacement, mechanical ventilation, or a diagnosis code with pneumonia or venous thromboembolism during admission. New onset conditions were defined as a first-time diagnosis code in relation to the TAVR admission with atrial fibrillation, left bundle branch block, or pacemaker implantation. All codes are provided in eTable 2.

Statistical analyses

Baseline characteristics and in-hospital events were described as frequencies and percentages or medians with interquartile range (IQR), as appropriate. Kaplan-Meier functions were used to assess cumulative mortality in groups stratified according to COPD status (yes/no), AE-COPD risk (low/high), and the combination of AE-COPD risk (low/high) and treatment intensity levels (none or short-term, mono/dual, triple therapy, or home oxygen). Crude and inverse probability of treatment weighted (IPW)[27] Cox regression models were used to estimate the hazard ratios (HRs) comparing subgroups of patients according to COPD severity status and the non-COPD patients. The IPW models were based on the following covariates with a known prognostic impact (directed acyclic graph is presented in eFigure 1): age groups (quartiles: <76, 76-80, 81-84, 85≤), sex, socioeconomic status (highest achieved educational level and marital status as a proxy for cohabitation), comorbidities (ischemic heart disease, congestive heart failure, hypertension, atrial fibrillation, diabetes mellitus, renal disease, liver disease, cerebrovascular disease, peripheral vascular disease, cancer, TAVR access type, previous PCI or CABG). Accounting for unbalanced baseline confounders, we also computed IPW Kaplan Meier failure functions to report adjusted 1-year mortality according to COPD severity groups. Further, among 1-year survivors, the number of days hospitalized the year after TAVR admission were displayed according to COPD severity subgroups (0, 1-14, 15-28, or 28< days). Lastly, the three most frequent causes of death (cardiovascular, respiratory, cancer) were reported as frequencies and percentages according to COPD status in a TAVR cohort from 2008-2018 due to availability of data on causes of death. The analyses were performed using SAS software 9.4 and R version 3.5.1.[28]

Sensitivity analyses

We repeated the analyses using any primary or secondary in- and out-patient diagnosis to identify patients with COPD to increase completeness of COPD status. To assess any confounding by unmeasured frailty as falls, poor mobility, or impaired mental function not measured in the primary Cox model, we conducted an adjusted Cox model including Hospital Frailty Risk Score groups, excluding comorbidities due to substantial overlap between conditions included in the risk score. To assess the importance of severe kidney disease, we repeated the adjusted analysis staging chronic kidney disease according to estimated glomerular filtration rate (eGFR: 0-29, 30-44, 45-59, 60≤ mL/min/1.73 m2) in the subgroup of patients undergoing TAVR with available creatinine levels.

Ethics

This study complied with the Declaration of Helsinki. Observational registry studies do not require ethical permission in Denmark. The use of data was approved by the Danish Data Protection Agency (Approval number: P-2019-191).

Results

Baseline characteristics and in-hospital events

After applying exclusion criteria, we identified 7,047 patients undergoing first-time TAVR between 1 January 2008 and 31 December 2021 (eFigure 1). Of these, 644 patients had a history with COPD (7.6%). The risk of AE-COPD was low among 439 patients with COPD and high among 205 patients. We observed comparable age and sex distributions between groups of patients without COPD and those with low or high risk of AE-COPD (Table I). The proportion of patients with concurrent comorbidities increased with increasing risk of AE-COPD with the lowest level among patients without COPD and the highest level among patients with high risk of AE-COPD (Table I). The baseline characteristics according to treatment intensity levels are summarized in eTable 3. Patients with high risk of AE-COPD had a slightly higher proportion of in-hospital pneumonia (4.9%) compared with the other two groups (No COPD: 1.5%, low risk of AE-COPD: 0.9%) (eTable IV).

One-year mortality

The median time of follow-up was equal in the groups (No COPD: 365 days (5th-95th percentiles: 87-365), low risk of AE-COPD: 365 days (5th-95th percentiles: 48-365), and high risk of AE-COPD: 365 days [5th-95th percentiles: 35-365]). As illustrated in Figure 1A, the cumulative 1-year mortality was 8.5% (95% CI: 7.8-9.2) for TAVR patients without COPD compared with 15.4% (95% CI:

Table I. Baseline characteristics for patients undergoing first-time TAVR according to COPD status

	No COPD	COPD	
		Low risk of AE-COPD	High risk of AE-COPD
Total, n (%)	6,403 (100)	439 (100)	205 (100)
Median age, years [IQR]	81.5 [77.0-82.1]	80.6 [75.4-84.7]	78.7 [73.8-83.1]
Sex (male), n (%)	3,574 (55.8)	237 (54.0)	113 (55.1)
Education, n (%)			
Basic school (lowest), ISCED 0-2	2,254 (35.2)	172 (39.2)	96 (46.8)
Higher education (highest), ISCED 7-8	219 (3.4)	11 (2.5)	<4
Living alone, n (%)	2,923 (45.6)	219 (49.9)	86 (42.0)
Comorbidities, n (%)			
Heart failure	1,562 (24.4)	127 (28.9)	77 (37.6)
Previous MI	621 (9.7)	35 (8.0)	21 (10.2)
Atrial fibrillation/flutter	1,671 (26.1)	116 (26.4)	65 (31.7)
Hypertension*	5,022 (78.4)	357 (81.3)	166 (81.0)
Diabetes†	1,368 (21.4)	108 (24.6)	57 (27.8)
Peripheral vascular disease	669 (10.4)	75 (17.1)	38 (18.5)
Cerebrovascular disease	534 (8.3)	31 (7.1)	19 (9.3)
Chronic kidney disease	427 (6.7)	49 (11.2)	23 (11.2)
Chronic dialysis	57 (0.9)	10 (2.3)	0 (0.0)
Liver disease	104 (1.6)	8 (1.8)	4 (2.0)
Cancer	941 (14.7)	60 (13.7)	40 (19.5)
Pulmonary fibrosis	45 (0.7)	9 (2.1)	5 (2.4)
Sleep apnea	59 (0.9)	7 (1.6)	4 (2.0)
COPD treatment intensity levels, n (%)			
No/short-term therapy	-	119 (27.1)	30 (14.6)
Mono/dual therapy	-	174 (39.6)	81 (39.5)
Triple therapy	-	124 (28.3)	74 (36.1)
Home oxygen,	-	22 (5.0)	20 (9.8)
Frailty risk score, n (%)			
Low	4,367 (68.2)	246 (56.0)	87 (42.4)
Intermediate	1,804 (28.2)	160 (36.5)	98 (47.8)
High	232 (3.6)	33 (7.5)	20 (9.8)
Blood samples, medians, [IQR]			
Hemoglobin, mmol/L	7.4 [6.6-8.1]	7.3 [6.5-8.0]	7.2 [6.3-7.9]
Missing	1,875 (29.2)	135 (30.8)	62 (30.2)
Albumin, g/L	36 [32-40]	35 [31-39]	36 [31-40]
Missing	2,493 (38.9)	178 (40.6)	72 (35.1)
Creatinine, µmol/L	87 [70-110]	88 [69.5-115]	70 [70-114]
Missing	1,855 (29.0)	135 (30.8)	60 (29.3)
Non-COPD hospitalizations 1-year prior index date, days‖			
0	3,401 (53.1)	251 (57.2)	113 (55.1)
1-14	1,205 (18.8)	76 (17.3)	32 (15.6)
15-28	217 (3.4)	19 (4.3)	14 (6.8)
28 <	1,580 (24.7)	93 (21.2)	46 (22.4)
Previous cardiac intervention, n (%)			
PCI	1,544 (24.1)	118 (26.9)	45 (22.0)
CABG	695 (10.8)	38 (8.7)	13 (6.3)

It is prohibited to report less than 3 observations with data from Statistics Denmark

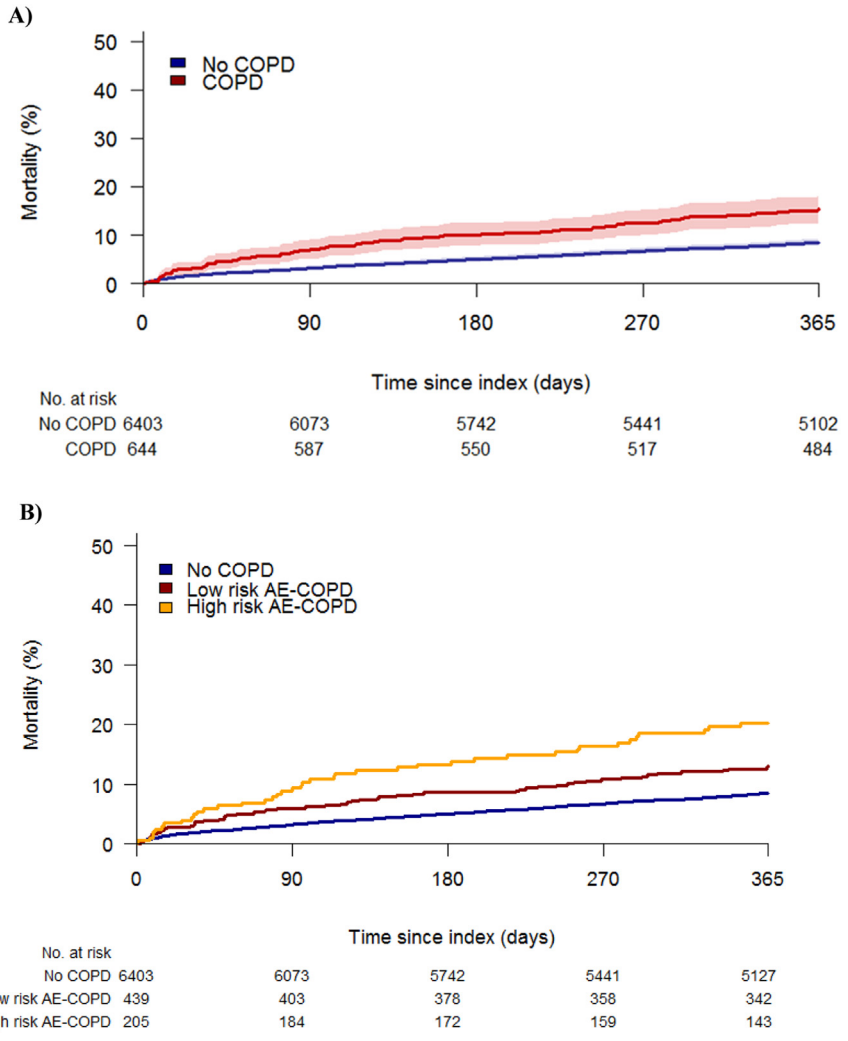
* Defined as redemption of ≥2 antihypertensive drugs 180 days before admission.

† Defined as an ICD-10 code with diabetes or any redeemed prescribed anti-diabetic drug 180 days before admission.

‖ COPD hospitalizations are a part of the AE-COPD definition.Abbreviations: AE-COPD, Acute exacerbation of chronic obstructive pulmonary disease; CABG, Coronary artery bypass grafting; COPD, Chronic obstructive pulmonary disease; IQR, Inter quartile range; ISCED, International Standard Classification of Education; PCI, Percutaneous coronary intervention.

12.5-18.2) for those with COPD (adjusted HR: 1.63 [95% CI: 1.28-2.07], Table II). Patients with low or high risk of AE-COPD had 1-year mortality of 13.1% (95% CI: 9.8-16.3) and 20.2% (95% CI: 14.6-25.8) (Figure 1B) with corresponding adjusted HRs of 1.31 (95% CI: 0.97-1.78) and 2.44 (95% CI: 1.70-3.50) compared with non-COPD patients (Table II). The mortality was similar in groups of patients with COPD stratified according to treatment intensity levels (eFigure 3, Table II). However, we observed that patients with high risk of AE-COPD and no/short term therapy or high risk of AE-COPD and use of home oxygen represented the subgroups of patients with the highest 1-year mortality of 31.6% (95% CI: 14.5-48.7) and 30.9% (95% CI: 10.3-51.6) (eFigure 3, Table II). The ad-

Figure 1



One-year cumulative mortality in patients undergoing TAVR by A, COPD status and B, AE-COPD severity level.

justed Kaplan-Meier functions, accounting for baseline differences between groups, were comparable with the unadjusted analyses (eFigure 4). Overall, cardiovascular causes accounted for most causes of death (COPD: 52.1% vs No COPD: 58.6%), however, markedly more patients with COPD died from respiratory diseases (20.6% vs 6.3%, eTable V).

Rehospitalization

The 1-year incidences of the composite of mortality or rehospitalization were 51.8% (95% CI: 50.5-53.0) for non-COPD patients undergoing TAVR and 68.0% (95% CI: 64.3-71.7) for patients with COPD (Figure 2A). The adjusted HR comparing patients with COPD with those without was 1.47 (95% CI: 1.32-1.64) (Table II). The corresponding results for patients with low or high risk of AE-COPD were 65.0% (95% CI: 60.4-69.6) and 74.3% (95% CI: 68.2-80.4) (Figure 2B, Table II). As shown in eFigure 5, patients with COPD were more hospitalized the year after TAVR compared with those without COPD and the number of days hospitalized increased with increasing risk of AE-COPD.

Sensitivity analyses

As displayed in eFigure 6, the results were consistent in the cohort in which COPD was defined by any primary or secondary in- and out-patient diagnoses. Furthermore, adjusted hazard ratios from the Cox model including the Hospital Frailty Risk Score groups were

Table II. Crude and adjusted hazard ratios for 1-year mortality and the composite of 1-year mortality or rehospitalization.

Patients undergoing TAVR	All-cause mortality		Mortality or rehospitalization	
	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
No COPD	1 (reference)	1 (reference)	1 (reference)	1 (reference)
COPD, all	1.90 (1.53-2.37)	1.63 (1.28-2.07)	1.52 (1.38-1.68)	1.47 (1.32-1.64)
COPD stratified according to AE-COPD risk				
No COPD	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Low risk	1.60 (1.21-2.12)	1.31 (0.97-1.78)	1.42 (1.26-1.60)	1.35 (1.18-1.54)
High risk	2.58 (1.87-3.57)	2.44 (1.70-3.50)	1.77 (1.51-2.06)	1.79 (1.52-2.12)
COPD stratified according to treatment intensity levels				
No COPD	1 (reference)	1 (reference)	1 (reference)	1 (reference)
No/short term therapy	2.24 (1.48-3.37)	1.85 (1.19-2.88)	1.69 (1.40-2.04)	1.62 (1.32-2.00)
Mono/dual therapy	1.74 (1.24-2.26)	1.66 (1.15-2.40)	1.42 (1.21-1.66)	1.38 (1.16-1.63)
Triple therapy	1.77 (1.20-2.60)	1.33 (0.85-2.07)	1.56 (1.32-1.85)	1.51 (1.24-1.82)
Home oxygen	2.40 (1.20-4.81)	2.14 (1.02-4.49)	1.47 (1.02-2.10)	1.41 (0.97-2.05)
COPD stratified according to AE-COPD risk and treatment intensity level				
No COPD	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Low risk – No/short term therapy	1.74 (1.05-2.89)	1.32 (0.76-2.78)	1.57 (1.26-1.95)	1.48 (1.17-1.89)
Low risk – Mono/dual therapy	1.68 (1.11-2.54)	1.51 (0.96-2.36)	1.30 (1.07-1.59)	1.23 (0.99-1.53)
Low risk – Triple therapy	1.45 (0.85-2.46)	1.11 (0.61-2.00)	1.52 (1.23-1.88)	1.47 (1.16-1.85)
Low risk – Home oxygen	1.11 (0.27-4.64)	1.00 (0.23-4.33)	1.08 (0.61-1.89)	1.05 (0.59-1.88)
High risk – No/short term therapy	4.53 (2.27-9.04)	4.58 (2.18-9.60)	2.24 (1.56-3.22)	2.38 (1.69-3.36)
High risk – Mono/dual therapy	1.89 (1.06-3.36)	2.07 (1.16-3.70)	1.67 (1.31-2.14)	1.73 (1.35-2.23)
High risk – Triple therapy	2.32 (1.34-4.02)	1.82 (0.92-3.62)	1.64 (1.25-2.14)	1.59 (1.15-2.20)
High risk – Home oxygen	3.92 (1.82-8.42)	3.62 (1.61-8.11)	2.02 (1.29-3.15)	2.00 (1.29-3.09)

AE-COPD: Acute exacerbation with chronic obstructive pulmonary disease, CI: Confidence intervals, HR: hazard ratio

*Adjusted using inverse probability weighting cox regression model including age groups (quartiles: <76, 76-80, 81-84, 85≤), sex, socio-economic status (highest achieved educational level and marital status as a proxy for cohabitation), comorbidities (ischemic heart disease, congestive heart failure, hypertension, atrial fibrillation, diabetes mellitus, renal disease, liver disease, cerebrovascular disease, peripheral vascular disease, cancer, TAVR access type, previous PCI or CABG.

similar to the main analyses (1-year adjusted HR for subgroups with COPD overall, low, and high risk of AE-COPD vs no COPD: 1.60 [95% CI: 1.25-2.04], 1.25 [95% CI: 0.91-1.69], and 2.52 [95% CI: 1.73-3.67]). Lastly, mortality for patients undergoing TAVR increased with increasing severity of kidney disease as shown in eFigure 7.

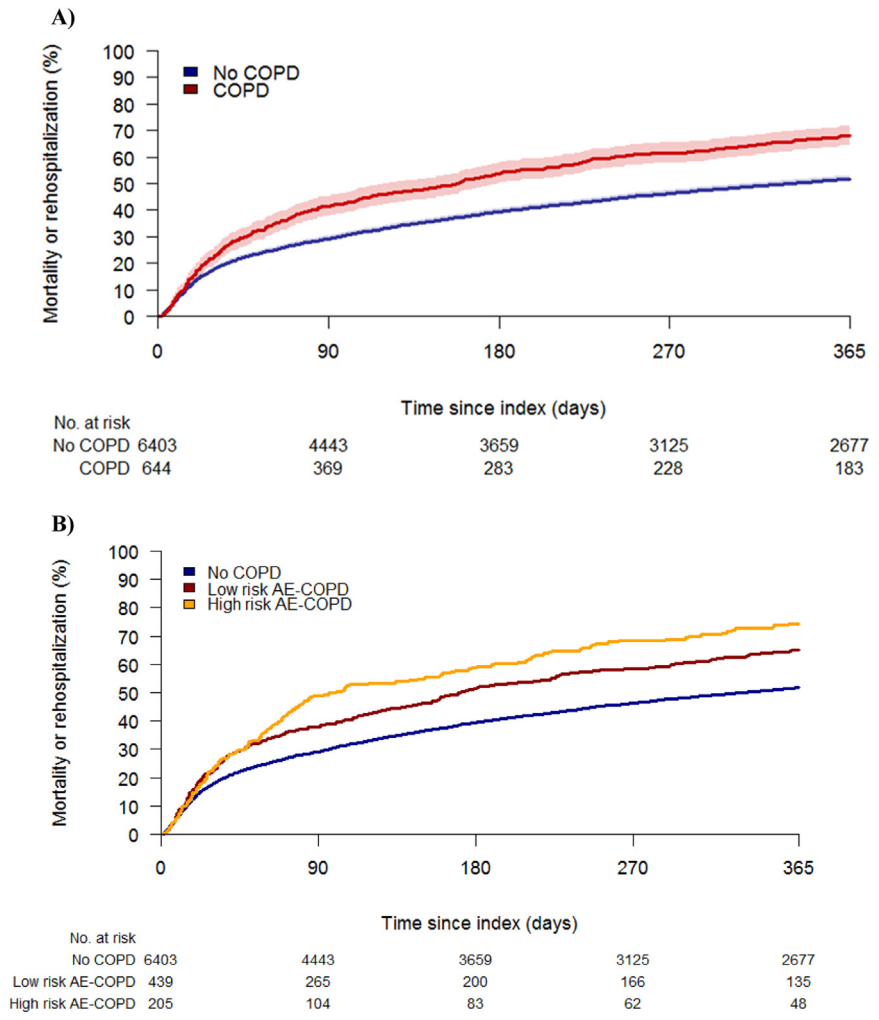
Discussion

In this nationwide cohort study, increasing risk of AE-COPD was associated with increasing all-cause mortality and burden of rehospitalizations after TAVR compared with non-COPD patients. Patients with high risk of AE-COPD not using any guideline recommended therapy and those using home oxygen represented the subgroups of TAVR patients with the poorest prognosis with a 1-year mortality exceeding 30%.

Mortality after TAVR: the importance of COPD

COPD is an independent predictor of morbidity and mortality among patients with symptomatic AS evaluated for intervention.[6,29] As such, patients with COPD are often treated with TAVR instead of SAVR as a less invasive alternative for surgical high-risk patients with an ongoing search for expanding indication across surgical risk groups.[30–32] Nevertheless, COPD is continuously associated with increased mortality in the TAVR era with a more than 50% increased mortality rate for patients with COPD undergoing TAVR compared with those without COPD.[4,10,33–35] In accordance with previous evidence,[4,10,35] we observed a markedly higher mortality and risk of rehospitalization after TAVR among patients with COPD compared with those without COPD in our contemporary and real-world cohort. One-year mortality was in this study lower for both non-COPD and COPD patients undergoing TAVR compared with previous COPD-TAVR studies (Non-COPD vs COPD.: Mok et al: 15.5%, vs 29.4%, Dvir et al.: 23.4% vs 19.6%).[4,10] Though, the prior studies had limited contemporality with inclusion of patients ending in 2009.[4,10] The mortality rate in year 2017 was 13.7% in the more recent study from Society of Thoracic Surgeons–American College of Cardiology Transcatheter Valve Therapy Registry.[36] The mechanisms underlying the increased long-term mortality after TAVR in

Figure 2



One-year cumulative incidence of the composite of mortality or rehospitalization in patients undergoing TAVR by A, COPD status and B, AE-COPD severity level.

relation to COPD are poorly understood with conflicting statements on long-term causes of death.[4,35] Still, pre-existing intrinsic patient factors (ie, severe renal, pulmonary, or cardiac dysfunction) has been suggested as independent predictors of mortality >3 years after TAVR rather than procedure related factors during the TAVR hospitalization.[37] In addition to COPD, chronic renal disease and frailty have been suggested as independently associated factors of poor outcomes post-TAVR.[9] In a sensitivity analysis accounting for concurrent renal disease, evaluated by eGFR level, we observed point estimates similar to the primary analysis, though, the estimates lost precision due to limited number of observations. Recognizing an association between COPD and frailty[38] and because frailty has been associated with poor outcome among patients undergoing TAVR,[39] we choose to assess any confounding by unmeasured frailty in a supplementary sensitivity analysis. COPD and frailty share commons risk factors as age and smoking along with similar pathophysiological mechanisms (i.e., increased inflammation potentially causing physical frailty by sarcopenia).[38] Still, the association between COPD and mortality was consistent in the analysis accounting for frailty.

Identification of subgroups with a futile outcome after TAVR

Emerging attention has been raised towards futility of TAVR[9] with evidence of independent predictors of poor outcome among patients with concurrent COPD

as oxygen dependency, impaired mobility, poor baseline spirometry, unplanned weight loss, falls within 6 months, and a Society of Thoracic Surgeons (STS) score > 7%.[4,10,33,34,40,41] Mok et al deemed TAVR as futile among 43% of patients with COPD defined by lack of survival or improvement in functional outcome within 6 months after the procedure.[4] The most important predictor of futility was a 6-minutes-walk test <170m.[4] Still, patients with COPD experienced improvements in functionality after TAVR – yet lesser than the non-COPD patients.[4] Notably, TAVR was superior to standard medical therapy also in patients with severe pulmonary disease.[10] To our knowledge, this study was the first to examine whether increasing risk of AE-COPD 1-year preceding TAVR was associated with an increasing mortality compared with patients without COPD. In line with our results, Doldi et al found similar association between severe COPD and poor outcome after TAVR assessing disease severity by pulmonary function at baseline.[41] Consistent with the observations by MOK et al,[4] medication intensity levels as a proxy for underlying COPD severity could not be used as independent prognostic markers to distinguish poor outcomes in a TAVR cohort. Importantly, patients with a high risk of AE-COPD not using guideline-recommended therapy and those using home oxygen were the subgroups of patients with the poorest prognosis with 1-year mortality exceeding 30%. AE-COPD is associated with progression of COPD, decline of lung function, poor health status and quality of life, increased mortality and risk of rehospitalization,[12] thus likely being the mechanisms underlying the poor prognosis among this subgroup of patients with COPD. Consistent with our observations, socio-economic vulnerability may cause the lack of adherence to guideline-recommended treatment despite high risk of AE-COPD leading to poorer prognosis.[42]

Clinical implications

We encourage that each patient with symptomatic AS and COPD is carefully evaluated by a multidisciplinary heart team.[43] In addition to already known prognostic markers, easily accessible knowledge on AE-COPD history along with current use of COPD medication as an indicator for COPD severity may aid the identification of patients who may not benefit from TAVR. Notably, our results emphasize that all patients with severe COPD should be in optimal guideline-recommended therapy before TAVR to distinguish between overlapping symptoms between AS and untreated COPD in the selection of candidates for intervention and to improve long-term outcomes.[12] Further studies are warranted to explore the mechanisms underlying the poor prognosis for patients with COPD undergoing TAVR along with identification of more prognostic markers.

Strength and limitations

The main strength of this study was the use of contemporary unselected data from a nationwide population-based cohort in a country providing tax-funded universal health care unaffected by socio-economic or insurance status.[15] The nationwide registries allow complete and long-term follow-up.[15] Furthermore, a validated definition of COPD was used with a positive predictive value of 92% minimizing the potential of misclassification between exposure groups.[21] We lacked information on important covariates as smoking, body mass index, spirometry at baseline, functional classification, and echocardiographic parameters. Additionally, the results may be prone to residual confounding as a result of misclassification of the parameters used in the sensitivity analyses (ie, frailty and renal disease). Moreover, the prevalence of COPD was lower in this study compared with previous studies because data on patients only treated for COPD in primary sector could not be included in our study population. Nevertheless, we believe our COPD definition based on patients with any in- or out-patient hospital contact are representative of the most severe cases of COPD. Thus, our observations may be applicable to other settings with patients with COPD evaluated for TAVR in countries with similar guideline-recommended approach to severe symptomatic AS.[43,44]

Conclusions

Among patients undergoing first-time TAVR, increasing risk of acute exacerbation with COPD was associated with increasing 1-year mortality and risk of rehospitalization after TAVR compared with non-COPD patients. Patients with high risk of COPD exacerbation not using any guideline recommended COPD medication and those with high risk of COPD exacerbation using home oxygen represented the subgroups of patients with the poorest prognosis with >30% 1-year mortality.

Authors' Contribution

MDL, JV, and EF conceived the study idea and designed the study. MD and EF established and designed the cohort. The analyses were carried out by MD, JES, and JV. All authors participated in the discussion and interpretation of the results. MDL organized the writing and wrote the initial drafts. All authors analyzed data and critically revised the manuscript for content and approved the final version. EF is the guarantor.

Data availability statement

The study is based on data from Statistics Denmark. Data access can be obtained by application to Statistics Denmark.

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Disclosures

Dr. Lauridsen has nothing to declare. Mr. Valentin has nothing to declare. Dr. Strange has nothing to declare. Dr. Jacobsen reports personal fees from AstraZeneca outside the submitted work. Dr. Møller Weinreich reports personal fees from Astra Zeneca, Chiesi, Novartis, Boehringer Ingelheim, Pfizer, GSK, and Orion pharma outside the submitted work. Dr. Johnsen reports personal fees from BMS and Pfizer, outside the submitted work. Dr. Køber reports personal fees from Novartis, BMS, and AstraZeneca, outside the submitted work. Dr. Fosbøl reports a grant from Novo Nordisk, outside the submitted work.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2023.04.016.

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