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Chronic Obstructive Pulmonary Disease in Patients Undergoing Transcatheter Aortic Valve Implantation

Insights on Clinical Outcomes, Prognostic Markers, and Functional Status Changes

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Objectives This study sought to determine the effects of chronic obstructive pulmonary disease (COPD) on clinical outcomes in patients undergoing transcatheter aortic valve implantation (TAVI) and to determine the factors associated with worse outcomes in COPD patients.

Background No data exist on the factors determining poorer outcomes in COPD patients undergoing TAVI.

Methods A total of 319 consecutive patients (29.5% with COPD) who underwent TAVI were studied. Functional status was evaluated by New York Heart Association (NYHA) functional class, Duke Activity Status Index, and the 6-min walk test (6MWT) at baseline and at 6 to 12 months. The TAVI treatment was considered futile if the patient either died or did not improve in NYHA functional class at 6-month follow-up.

Results Survival rates at 1 year were 70.6% in COPD patients and 84.5% in patients without COPD ($p = 0.008$). COPD was an independent predictor of cumulative mortality after TAVI (hazard ratio: 1.84; 95% confidence interval: 1.08 to 3.13; $p = 0.026$). Improvement in functional status was observed after TAVI ($p < 0.001$ for NYHA functional class, Duke Activity Status Index, and 6MWT), but COPD patients exhibited less ($p = 0.036$) improvement in NYHA functional class. Among COPD patients, a shorter 6MWT distance predicted cumulative mortality ($p = 0.013$), whereas poorer baseline spirometry results (FEV_1 [forced expiratory volume in the first second of expiration]) determined a higher rate of periprocedural pulmonary complications ($p = 0.040$). The TAVI treatment was futile in 40 COPD patients (42.5%) and a baseline 6MWT distance <170 m best determined the lack of benefit after TAVI ($p = 0.002$).

Conclusions COPD was associated with a higher rate of mortality at mid-term follow-up. Among COPD patients, a higher degree of airway obstruction and a lower exercise capacity determined a higher risk of pulmonary complications and mortality, respectively. TAVI was futile in more than one-third of the COPD patients, and a shorter distance walked at the 6MWT predicted the lack of benefit after TAVI. These results may help to improve the clinical decision-making process in this challenging group of patients. (J Am Coll Cardiol Intv 2013;6:1072–84) © 2013 by the American College of Cardiology Foundation

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Chronic obstructive pulmonary disease (COPD) is a pulmonary condition characterized by chronic airflow limitation that is not fully reversible. In the management of patients with severe aortic stenosis, COPD is present in ~19% of patients amenable to surgical aortic valve replacement (SAVR) (1). In the past decade, transcatheter aortic valve implantation (TAVI) has emerged as an alternative to SAVR in patients considered to be either inoperable or at very high surgical risk. COPD is one of the main comorbidities leading to patients' inoperability in cardiac surgery, and it is therefore not surprising that as many as 28% to 43% of the patients undergoing TAVI have comorbid COPD (2–8).

In TAVI, COPD has been identified as a risk factor for mortality (4,7,9), but no data exist to date on the prognostic markers for periprocedural pulmonary complications or mortality in this subgroup. A better knowledge of the factors determining poorer outcomes in COPD patients would be of major importance to improve both patient selection and perioperative management. In pulmonary medicine, studies of patients with COPD have identified a number of prognostic markers for all-cause mortality (10,11), death from respiratory causes, as well as hospitalization for acute exacerbations (12). These factors include increased age, body mass index (BMI), severity of airway obstruction (forced expiratory volume in the first second of expiration [FEV_1]), and exercise capacity (6-min walk test [6MWT]); however, the prognostic value of these 4 factors in COPD patients undergoing TAVI has not been evaluated. Furthermore, patients have significant improvement in functional status and quality of life (13,14) after TAVI, but little is known about whether patients with COPD experience a similar level of improvement. The objectives of our study were 2-fold: 1) to determine the effects of COPD on clinical outcomes and functional status; and 2) to evaluate the factors that predict pulmonary complications, mortality, and treatment futility in patients with COPD undergoing TAVI.

Methods

Study population and TAVI procedures. A total of 319 consecutive patients who underwent TAVI were studied. Details of the evaluation process and the TAVI procedure were described previously (4). In brief, a multidisciplinary team that included 2 interventional cardiologists and 2 cardiac surgeons evaluated all potential TAVI candidates. Depending on the degree of calcification, size of the iliofemoral arteries and severity of disease in the iliofemoral arteries: transfemoral (TF) or transapical (TA)/transaortic (TAo) approach were selected. All procedures were performed with patients under general anesthesia and with transesophageal echocardiography guidance. Data on procedural success and major periprocedural complications as defined by Valve Academic Research Consortium (VARC) (15) were prospectively collected on pre-set data collection forms. In-hospital pulmonary complications were recorded and defined as the occurrence of either nosocomial pneumonia or respiratory failure necessitating re-intubation and/or tracheotomy.

Functional status assessment: New York Heart Association functional class, Duke Activity Status Index, and 6MWT. Functional status evaluation was performed at baseline (within the month before TAVI), at 6- to 12-month follow-up, and then yearly. The Duke Activity Status Index (DASI) questionnaire is a 12-item scale ranging from 0 (worst) to 58.2 (best) that evaluates the ability to perform common activities of daily living (Fig. 1) (16). The 6MWT was performed in accordance with the American Thoracic Society protocol (17) using a 30-m internal flat corridor marked by 2 orange traffic cones. Baseline 6MWT was not performed in 23 patients because of logistic reasons (6 patients with COPD). Baseline 6MWT was performed in 258 patients, and 38 patients unable to walk (distance = 0 m; 11 patients with COPD) due to medical reasons (New York Heart Association [NYHA] functional class IV [n = 11], severely limited mobility [n = 21], and recent myocardial infarction [n = 6]) were also included in the baseline 6MWT analysis. A significant improvement in functional class (baseline vs. follow-up) was defined as a decrease of at least 1 NYHA functional class or an increase of >10% in DASI score or 6MWT distance.

COPD assessment. COPD was defined according to Society of Thoracic Surgeons (STS) definition, which is based on spirometry results (FEV_1 <75% predicted) and/or requirement for bronchodilator therapy. Information on bronchodilator therapies, long-term oral corticosteroid therapy, and home oxygen therapy was recorded.

Follow-up. Clinical follow-up was conducted by clinical visits and/or phone consultation. Patients were followed at 1, 6, and 12 months and annually thereafter, and no patient was lost to follow-up. The occurrence of death during the follow-up period was recorded and further classified as

Abbreviations and Acronyms

6MWT = 6-min walk test
BMI = body mass index
CI = confidence interval
COPD = chronic obstructive pulmonary disease
DASI = Duke Activity Status Index
eGFR = estimated glomerular filtration rate
FEV_1 = forced expiratory volume in the first second of expiration
HR = hazard ratio
IQR = interquartile range
NYHA = New York Heart Association
ROC = receiver-operating characteristic
SAVR = surgical aortic valve replacement
STS = Society of Thoracic Surgeons
TA = transapical
TAo = transaortic
TAVI = transcatheter aortic valve implantation
TF = transfemoral
VARC = Valve Academic Research Consortium

Item	Activity	Weight
1	Can you take care of yourself (eating, dressing, bathing or using the toilet)?	2.75
2	Can you walk indoors, such as around your house?	1.75
3	Can you walk a block or two on level ground?	2.75
4	Can you climb a flight of stairs or walk up a hill?	5.50
5	Can you run a short distance?	8.00
6	Can you do light work around the house like dusting or washing dishes?	2.70
7	Can you do moderate work around the house like vacuuming, sweeping floors, or carrying in groceries?	3.50
8	Can you do heavy work around the house like scrubbing floors, or lifting and moving heavy furniture?	8.00
9	Can you do yardwork like raking leaves, weeding or pushing a power mower?	4.50
10	Can you have sexual relations?	5.25
11	Can you participate in moderate recreational activities like golf, bowling, dancing, doubles tennis, or throwing a baseball or football?	6.00
12	Can you participate in strenuous sports like swimming, singles tennis, football, basketball or skiing?	7.50

Figure 1. The DASI Questionnaire

The DASI questionnaire is a 12-item scale ranging from 0 (worst) to 58.2 (best) that evaluates the ability to perform common activities of daily living. Reprinted with permission from Hlatky et al. (16). DASI = Duke Activity Status Index.

cardiovascular (VARC criteria) or noncardiovascular. The TAVI treatment was considered futile if death or a lack of improvement in NYHA functional class occurred during the 6 months of follow-up.

Statistical analysis. Continuous variables are presented as mean ± SD or median (25th to 75th interquartile range [IQR]) depending on variable distribution. Group comparisons were tested for differences with the Student *t* test (paired Student *t* test for paired comparisons) or the Wilcoxon test for continuous variables, and the chi-square or Fisher exact test was used for categorical variables. Comparisons of clinical outcomes between COPD and no-COPD groups were adjusted for baseline differences between groups using a logistic regression analysis that included variables with a p value <0.05 on univariate analysis. Baseline and procedural variables exhibiting a p value <0.10 on univariate analysis were included in a logistic regression analysis or a Cox multivariate analysis to determine the predictive factors of cumulative overall mortality. The variables included in the multivariate analysis were sex, chronic atrial fibrillation, estimated glomerular filtration rate (eGFR) <60 ml/min, COPD, peripheral vascular disease, 6MWT, mean aortic gradient, left ventricular ejection fraction, and TA/TAo approach. In the COPD-TAVI cohort, baseline and procedural variables exhibiting a p value <0.05 were included in a logistic regression analysis or Cox multivariate analysis to determine the predictive factors of periprocedural pulmonary complications, cumulative overall mortality and futility. The variables included in the analysis for the prediction of pulmonary complications were: sex, FEV1, and oxygen dependency. The variables included in the multivariate analysis for the prediction of cumulative overall mortality were: eGFR <60 ml/min, DASI, and 6MWT. The variables included in the prediction of treatment futility were: eGFR <60 ml/min and 6MWT. Model performance was evaluated using Hosmer-Lemeshow goodness-of-fit test for logistic regression models and Martingale residual plots for Cox proportional hazards models. Receiver-operating characteristic (ROC) curve analysis (greatest sum of sensitivity and specificity) was used to discriminate threshold values of 6MWT and FEV_1 to clinical outcomes. Survival curves up to 1 year were presented as Kaplan-Meier curves, and the log-rank test was used for comparison between groups. A 2-way analysis of variance or analysis of covariance for repeated measures, followed by a Tukey post-hoc test was used to evaluate the effects of time (baseline vs. discharge vs. follow-up) and group (COPD vs. no COPD) on Doppler echocardiographic variables. The results were considered significant with p values <0.05. All analyses were conducted using the SAS statistical package version 9.3 (SAS Institute Inc., Cary, North Carolina).

Results

Of the 319 patients who underwent TAVI, 94 (29.5%) had a diagnosis of COPD, with a mean FEV_1 of 60 ± 21% and requiring a median of 2 (IQR: 1 to 3) inhaled bronchodilator medications. Ten patients (10.6%) received long-term oral glucocorticosteroid therapy and 8 patients (8.5%) were home oxygen dependent. Baseline and procedural characteristics of the study population, according to the presence of COPD, are shown in Table 1.

30-day and late outcomes. Clinical outcomes after TAVI, grouped according to the presence of COPD, are shown in

Table 1. Baseline and Procedural Characteristics of the Study Population According to the Presence of COPD

		COPD		
	Study Population (N = 319)	No (n = 225)	Yes (n = 94)	p Value
Baseline variables				
Age, yrs	80 ± 8	80 ± 8	78 ± 8	0.053
Male	147 (46.1)	89 (39.6)	58 (61.7)	<0.0001
BMI, kg/m^2	26.8 ± 5.4	26.4 ± 5.2	27.8 ± 5.7	0.039
NYHA functional class				
I-II	63 (19.7)	53 (23.6)	10 (10.7)	0.008
III-IV	256 (80.3)	172 (76.4)	84 (89.4)	
Smoker				
Current	15 (4.7)	7 (3.1)	8 (8.5)	0.041
Previous	80 (25.1)	47 (20.9)	33 (35.1)	0.011
Diabetes	119 (37.3)	66 (29.3)	43 (45.7)	0.006
Hypertension	284 (89.0)	198 (88.0)	86 (91.5)	0.435
CAD	204 (63.9)	145 (64.4)	59 (62.8)	0.799
Previous MI	112 (35.1)	80 (35.6)	32 (34.0)	0.898
Previous AF	98 (30.7)	68 (30.2)	30 (31.6)	0.791
Previous CABG	123 (38.6)	85 (37.8)	38 (40.4)	0.706
Previous stroke	61 (19.1)	40 (17.8)	21 (22.3)	0.352
Peripheral vascular disease	111 (34.8)	63 (28.0)	48 (51.1)	<0.0001
eGFR <60 ml/min	192 (60.2)	147 (65.3)	45 (47.9)	0.004
STS-PROM score	6.3 (4.1–8.9)	5.8 (3.8–8.3)	7.5 (5.5–10.3)	<0.0001
Frailty	63 (19.8)	52 (23.1)	11 (11.7)	0.021
6MWT, m*	163 (62–253)	159 (63–250)	168 (60–267)	0.525
Echocardiographic variables				
Mean aortic gradient, mm Hg	40 ± 16	42 ± 17	38 ± 12	0.026
Aortic valve area index, cm^2/m^2	0.24 (0.20–0.30)	0.24 (0.20–0.29)	0.25 (0.21–0.30)	0.229
LVEF, %	54 ± 14	54 ± 14	53 ± 15	0.919
SPAP, mm Hg	40 (33–50)	39 (32–47)	47 (35–55)	0.001
Procedural characteristics				
Approach				
TF	125 (39.2)	94 (41.8)	31 (32.9)	0.167
TA/Tao	194 (60.8)	131 (58.2)	63 (67.0)	
Prosthesis type				
Edwards SAPIEN†	183 (57.4)	128 (56.9)	55 (58.5)	0.366
Edwards SAPIEN XT†	124 (38.9)	89 (39.6)	35 (37.2)	
Edwards SAPIEN 3†	8 (2.5)	4 (1.8)	4 (4.3)	
St. Jude Medical PORTICO‡	4 (1.3)	4 (1.8)	0 (0.0)	
Prosthesis size, mm				
20	1 (0.3)	1 (0.4)	0 (0.0)	0.075
23	169 (52.9)	129 (57.3)	40 (42.6)	
26	124 (38.9)	79 (35.1)	45 (48.0)	
29	25 (7.9)	16 (7.1)	9 (9.7)	
Procedural success	284 (89.0)	205 (91.1)	79 (84.0)	0.073

Values are mean ± SD, n (%), or median (interquartile range). *Data from 296 patients; 88 patients in the COPD group. †Edwards Lifesciences, Irvine, California. ‡St. Jude Medical, St. Paul, Minnesota.

6MWT = 6-min walk test; AF = atrial fibrillation; BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; COPD, chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; STS-PROM = Society of Thoracic Surgeons predicted risk of mortality; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; SPAP = systolic pulmonary artery pressure; TA/TAo = transapical/transaortic; TF = transfemoral.

Table 2. The 30-day mortality rates were similar between groups (9.6% vs. 7.1%, p = 0.578). There were no significant differences in VARC-defined complications between COPD and no-COPD patients; however COPD patients had a higher rate of pulmonary complications (27.7% vs. 4.5%, p < 0.0001).

Table 2. 30-Day and Late Outcomes, According to the Presence of COPD

	Study Population (N = 319)	COPD		OR/HR (95% CI)*	p Value
		No (n = 225)	Yes (n = 94)		
30-day outcomes					
MI	4 (1.3)	2 (0.9)	2 (2.1)	2.42 (0.34–17.5)	0.380
Stroke	10 (3.1)	8 (3.6)	2 (2.1)	0.59 (0.12–2.83)	0.509
Major bleeding	34 (10.7)	20 (8.9)	14 (14.9)	1.82 (0.82–4.07)	0.141
Pulmonary complications	36 (11.4)	10 (4.5)	26 (27.7)	7.33 (3.11–17.3)	<0.0001
Pneumonia	33 (10.4)	9 (4.0)	24 (25.5)	7.05 (2.87–17.3)	<0.0001
Respiratory failure requiring re-intubation or tracheostomy	19 (5.9)	7 (3.1)	12 (12.8)	3.99 (1.39–11.45)	0.0100
Mortality	25 (7.8)	16 (7.1)	9 (9.6)	1.32 (0.51–3.30)	0.578
Length of stay, days	7 (5–10)	7 (5–9)	7 (5–14)	—	0.133
Follow-up (>30 days) outcomes					
MI	7 (2.2)	3 (1.4)	4 (4.4)	6.23 (1.20–32.4)	0.029
Stroke	4 (1.3)	3 (1.4)	1 (1.1)	0.89 (0.24–3.27)	0.854
Mortality (>30 days)	69 (21.6)	41 (18.2)	28 (29.8)	1.71 (0.98–3.00)	0.036
Cardiovascular mortality	32 (10.0)	21 (9.3)	11 (11.7)	1.35 (0.65–2.80)	0.428
Noncardiovascular death	37 (11.6)	20 (8.9)	17 (18.1)	2.18 (1.14–4.17)	0.019
Respiratory	14 (4.4)	2 (0.9)	12 (12.8)	13.52 (3.01–60.6)	0.0007
Malignancy	8 (2.5)	6 (2.9)	2 (2.1)	0.98 (0.20–4.85)	0.978
Renal failure	5 (1.7)	3 (1.4)	2 (2.1)	1.62 (0.27–9.77)	0.267
Multiorgan failure	2 (0.7)	1 (0.5)	1 (1.2)	2.75 (0.17–44.1)	0.199
Gastrointestinal tract defect	4 (1.4)	4 (1.9)	0 (0.0)	—	0.328
Nonrespiratory sepsis	4 (1.4)	4 (1.9)	0 (0.0)	—	0.328
Cumulative outcomes					
MI	11 (3.5)	5 (2.2)	6 (6.4)	3.24 (0.77–13.7)	0.109
Stroke	14 (4.4)	11 (4.9)	3 (3.2)	0.80 (0.19–3.44)	0.768
Overall mortality	94 (29.5)	57 (25.3)	37 (39.4)	1.63 (1.02–2.60)	0.042
Cardiovascular mortality	46 (14.4)	29 (12.9)	17 (18.1)	1.34 (0.68–2.62)	0.396
Noncardiovascular death	48 (15.1)	28 (12.4)	20 (21.3)	1.95 (1.02–3.75)	0.044
Respiratory	19 (5.9)	6 (2.7)	13 (13.8)	6.17 (2.04–18.6)	0.001
Malignancy	8 (2.5)	6 (2.7)	2 (2.1)	1.38 (0.23–8.23)	0.726
Renal failure	5 (1.6)	3 (1.3)	2 (2.1)	4.01 (0.34–46.7)	0.268
Multiorgan failure	5 (1.6)	4 (1.8)	1 (1.1)	0.72 (0.07–7.19)	0.776
Gastrointestinal tract defect	6 (1.9)	5 (2.2)	1 (1.1)	0.65 (0.06–6.59)	0.713
Nonrespiratory sepsis	5 (1.6)	4 (1.8)	1 (1.1)	0.42 (0.04–4.52)	0.477

Values are n (%) or median (25th to 75th, interquartile range). *Values are expressed as OR for 30-day outcomes and HR for follow-up (>30-day) outcomes and cumulative outcomes; p value refers to the significance of the logistic regression analysis (OR) or Cox proportional hazard regression (HR).

CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; OR = odds ratio.

Median follow-up was 12 months (IQR: 7 to 25 months), with no differences between groups (COPD: 12 months [IQR: 7 to 25 months] vs. no COPD: 12 months [IQR: 7 to 25 months], p = 0.614). A higher rate of late (>30-day) mortality was observed in COPD patients (29.8% vs. 18.2%, p = 0.036), and this was related to a higher rate of noncardiac death caused by respiratory failure in COPD patients (12.8% vs. 0.9%, p < 0.001). Cumulative mortality was significantly higher in COPD patients compared with no-COPD patients (39.4% vs. 25.3%, p = 0.042). Kaplan-Meier survival curves at 1-year follow-up are shown in Figure 2. The 1-year survival rate was significantly lower in COPD-TAVI patients compared with patients without COPD (log-rank: 0.008) (Fig. 2). The rate of rehospitalization for noncardiovascular causes at 1-year follow-up was also much higher in COPD patients compared with the rest of the study population (log-rank: 0.028) (Fig. 2).

The variables associated with a higher cumulative mortality are shown in Table 3. COPD was associated with a higher cumulative mortality rate on univariate analysis (hazard ratio [HR]: 1.69; 95% confidence interval [CI]: 1.11 to 2.55; p = 0.014) and was identified as an independent

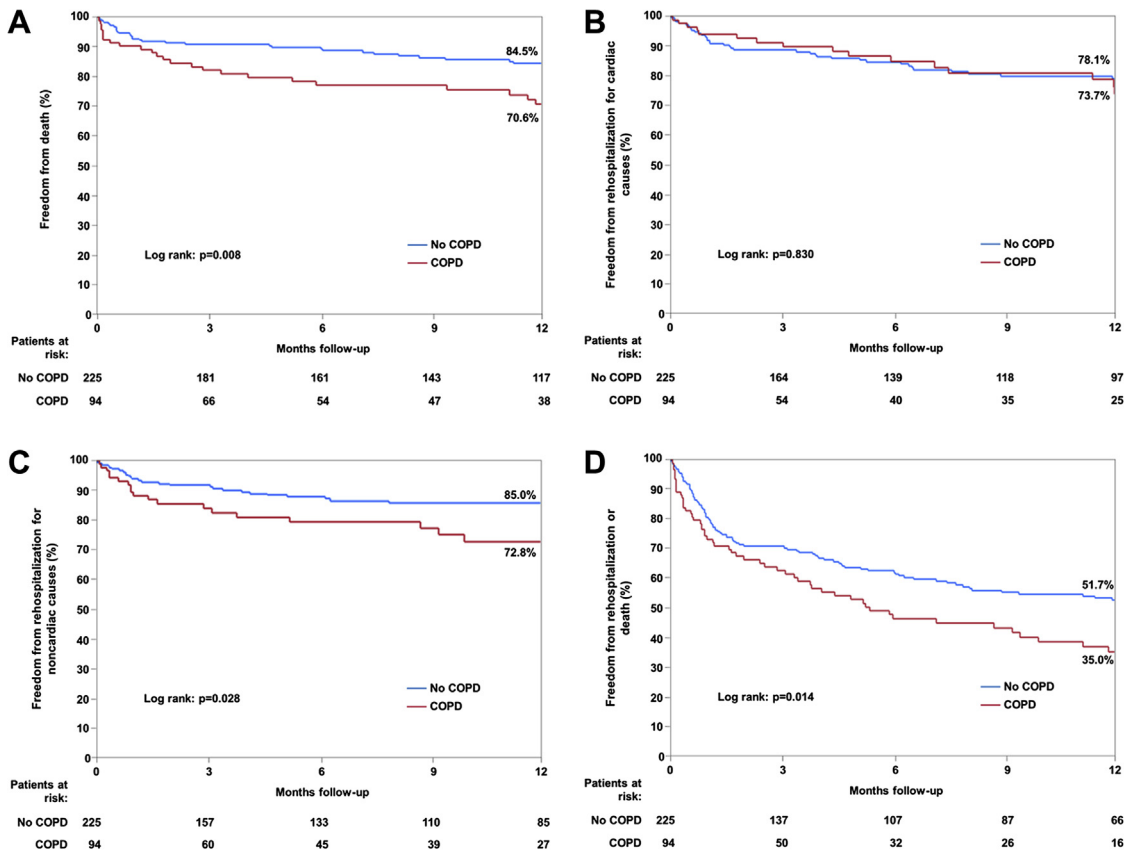

Figure 2. Kaplan-Meier Curves at 1-Year Follow-up According to the Presence of COPD

(A) Freedom from death. **(B)** Freedom from rehospitalization for cardiovascular causes. **(C)** Freedom from rehospitalization for noncardiovascular causes. **(D)** Freedom from death or rehospitalization. COPD = chronic obstructive pulmonary disease.

predictor of cumulative late mortality in the multivariate analysis (HR: 1.84; 95% CI: 1.08 to 3.13; p = 0.026).

The echocardiographic results (valve hemodynamics, pulmonary artery systolic pressure) of the study population and according to the presence of COPD are shown in Figure 3.

Functional status changes after TAVI. All TAVI patients alive at 6 months had a NYHA functional class completed at follow-up. DASI questionnaires were available in 228 patients at baseline and at follow-up (172 no-COPD patients, 56 COPD patients). Of the 258 patients with a 6MWT performed at baseline, 183 were alive and had a minimum follow-up of 6 months, and of these, 156 patients (85%) had a 6MWT performed at 6 to 12 months (120 no-COPD patients, 36 COPD patients). The changes in functional status according to the presence of COPD are shown in Table 4. As many as 80% of patients had improved in NYHA functional class, but the rate of improvement was lower (p = 0.036) in COPD patients (71.6%) compared with non-COPD patients (83.7%) (Table 4, Fig. 4). Functional status as evaluated by DASI improved in 72% of the patients, with no differences between COPD and no-COPD groups (Table 4). Most (72%) patients improved their 6MWT distance, without differences between COPD and no-COPD groups (Table 4).

Prognostic factors in COPD patients. Twenty-six of the 94 COPD patients (27.7%) had pulmonary complications after TAVI. The variables associated with the occurrence of periprocedural (30-day) pulmonary complications after TAVI among COPD patients are shown in Table 5. Male sex (p = 0.027), a lower FEV_1 (p = 0.018), and oxygen dependence (p = 0.026) were associated with a higher rate of pulmonary complications on univariate analysis. The rate of pulmonary complications tended to be lower in TF compared with TA/TAo patients (16.1% vs. 33.3%, p = 0.10). On multivariate analysis, only a higher degree of airway obstruction as determined by FEV_1 was independently associated with a higher rate of pulmonary complications (odds ratio: 1.18 for each FEV_1 decrease of 5%; 95% CI: 1.02 to 1.38; p = 0.040) (Hosmer-Lemeshow goodness-of-fit

Table 3. Univariate and Multivariate Predictors of Cumulative Overall Mortality (n = 94 Events) in the Study Population (N = 319 Patients)

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Baseline variables				
Age, yrs*	1.00 (0.97–1.02)	0.699		
Male	1.75 (1.17–2.64)	0.016	1.98 (1.15–3.42)	0.013
BMI, kg/m^2†	1.05 (1.00–1.10)	0.114		
Smoker	1.11 (0.89–1.39)	0.351		
Diabetes	1.20 (0.79–1.83)	0.403		
Hypertension	1.29 (0.60–2.79)	0.520		
CAD	1.35 (0.87–2.10)	0.177		
Previous MI	1.39 (0.92–2.08)	0.116		
Previous AF	1.84 (1.22–2.79)	0.004	1.36 (0.81–2.28)	0.246
Previous CABG	1.07 (0.71–1.61)	0.761		
Previous stroke	0.26 (0.04–1.63)	0.150		
Peripheral vascular disease	1.45 (0.96–2.17)	0.075	0.89 (0.52–1.51)	0.664
eGFR <60 ml/min	1.60 (1.02–2.48)	0.039	1.19 (0.69–2.05)	0.531
COPD	1.69 (1.11–2.55)	0.014	1.84 (1.08–3.13)	0.026
Frailty	1.04 (0.60–1.82)	0.882		
6MWT, m‡	1.10 (1.05–1.16)	<0.001	1.11 (1.05–1.17)	0.004
Echocardiographic variables				
Mean aortic gradient, mm Hg*	0.98 (0.97–0.99)	0.004	0.99 (0.99–1.01)	0.113
Aortic valve area index, cm^2/m^2†	1.94 (0.87–4.32)	0.110		
LVEF, %*	0.99 (0.98–1.00)	0.094	1.00 (0.98–1.02)	0.990
SPAP, mm Hg*	1.01 (0.99–1.03)	0.125		
Procedural characteristics				
Approach TA/Tao	1.79 (1.09–2.94)	0.022	2.02 (1.04–3.95)	0.039
Procedural success	0.22 (0.03–1.59)	0.220		

*For each increase by 1 U. †For each decrease by 1 log-transformed unit. ‡For each decrease in 6MWT by 20 m (data from 296 patients). Abbreviations as in Tables 1 and 2.

test: 6.31 with 8 df, p = 0.612). FEV_1 <60% of predicted was identified as the cutoff point with the best sensitivity and specificity for the prediction of pulmonary complications after TAVI in COPD patients, with an area under the ROC curve of 0.67 (95% CI: 0.54 to 0.79; p = 0.026). Furthermore, COPD patients who experienced periprocedural pulmonary complications had a higher 30-day mortality (19.2% vs. 5.9%, p = 0.047).

Thirty-seven COPD patients (39.4%) had died at follow-up. The variables associated with a higher mortality after TAVI among COPD patients are shown in Table 6. On multivariate analysis, only a shorter distance walked in the 6MWT determined a higher risk of mortality (HR: 1.16 for each decrease in 20 m [95% CI: 1.06 to 1.27]), p = 0.013). A distance <150 m on the 6MWT was identified as the cutoff point for the prediction of cumulative death after TAVI in COPD patients, with an area under the ROC curve of 0.74 (95% CI: 0.63 to 0.84; p < 0.001). As many as 75% of the patients who walked <150 m before TAVI died at follow-up compared with 23.5% of the patients who walked ≥150 m (p < 0.001).

The TAVI treatment was considered futile (death or no improvement in functional status at 6-month follow-up) in 40 COPD patients (42.5%). The clinical characteristics of these patients compared with those who benefitted from the TAVI treatment are presented in Table 7. On multivariate analysis, a shorter distance walked in the baseline 6MWT determined a higher risk for treatment futility (odds ratio: 1.16 [IQR: 1.02 to 1.19]; p = 0.011) (Hosmer-Lemeshow goodness-of-fit test: 6.07 with 7 df, p = 0.532). A distance <170 m walked in the 6MWT was identified as the best cutoff point for the prediction of treatment futility, with an area under the ROC curve of 0.67 (95% CI: 0.55 to 0.78; p = 0.002). The TAVI treatment was futile in 59.1% of the patients who walked <170 m before TAVI compared with 28.6% of the patients who walked ≥170 m (p = 0.005).

A total of 16 COPD patients were either oxygen dependent (n = 6), on long-term steroid therapy (n = 8), or both (n = 2). The incidence of 30-day pulmonary complications and mortality in these patients was 50% and 6.3%, respectively (62.5% and 12.5%, respectively, for those

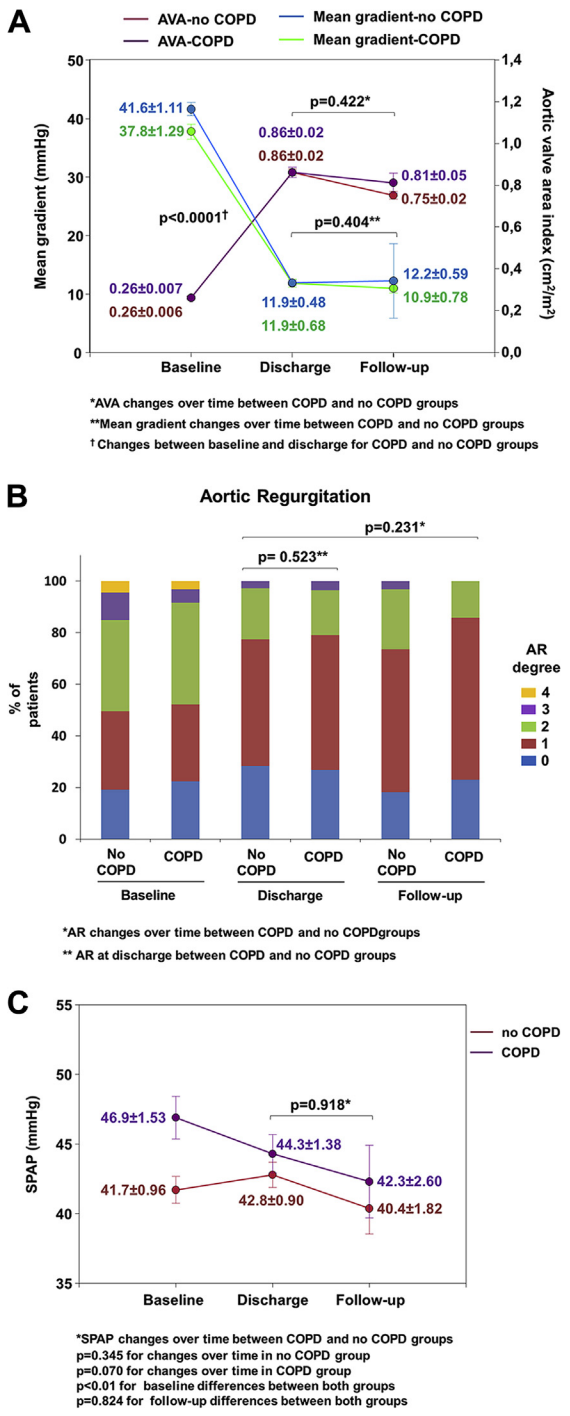

Figure 3. Valve Hemodynamics and Pulmonary Artery Systolic Pressure Changes After Transcatheter Aortic Valve Implantation According to the Presence of COPD

(A) Changes in mean gradient and aortic valve area after transcatheter aortic valve implantation. **(B)** Presence and degree of aortic regurgitation after transcatheter aortic valve implantation. **(C)** Changes in pulmonary artery pressure after TAVI. AR = aortic regurgitation; AVA = aortic valve area; COPD = chronic obstructive pulmonary disease; SPAP = systolic pulmonary artery pressure.

oxygen dependent). After a median follow-up of 17 (IQR: 6 to 35) months, 8 of these 16 patients had died (50%; 62.5% of those oxygen dependent).

Discussion

COPD as a predictor of mortality. Several TAVI registries and series have shown a relationship between COPD and mortality (4,7,9) at up to 1-year follow-up. Moderate to severe COPD remains an important reason for not performing SAVR in elderly patients with severe aortic stenosis, and it is thought that TAVI might be offered as a lower risk alternative for the treatment of this group of patients. This would explain the high rate (~30%) (2–9) of COPD patients in TAVI studies. In accordance with the results of previous TAVI studies, COPD appeared as one of the most important predictors of mortality at mid-term follow-up in our study, with a >1.5-fold higher risk of death among COPD patients. Respiratory failure has been identified as one of the main causes of late mortality after TAVI (4,6), but no studies to date have focused on the causes of death in COPD patients undergoing TAVI. The present study showed that most COPD patients died either because of pulmonary complications during the periprocedural period or at mid-term because of respiratory failure secondary to COPD. These results therefore highlight the importance of determining the factors associated with poorer outcomes in this high-risk group of patients.

Impact of COPD on functional status after TAVI. Previous studies have shown that TAVI results in improvement in quality of life and functional performance status (13,14). However, it has been shown that one-fifth to one-third of patients fail to achieve a significant improvement in functional status and/or quality of life (13,14,18), and one may wonder whether the presence of COPD may determine a higher risk of this lack of improvement. The results of our study showed a significant improvement in functional status as evaluated by NYHA functional class, DASI score, and 6MWT after TAVI. Although COPD patients exhibited similar improvements in DASI score and 6MWT as the rest of the study population, they had a higher NYHA functional class at baseline and failed to achieve comparable improvement in their NYHA functional class at follow-up. In accordance with our findings, De Blois et al. (19) showed that heart failure patients with COPD were overrated in terms of NYHA functional class compared with patients with a similar left ventricular ejection fraction, a reflection of poorer exercise tolerance as a result of impaired lung function in COPD patients.

Predictors of poorer outcomes among COPD patients. In respiratory medicine, studies of COPD patients have developed a number of risk assessment tools for morbidity and mortality. Celli et al. (10) introduced a risk score system (BODE Index) incorporating risk factors associated with

Table 4. Functional Changes at 6- to 12-Month Follow-up According to the Presence of COPD

	COPD		
	No	Yes	p Value
ΔNYHA class*			
Worsening/no change	33 (16.3)	21 (28.4)	0.036
Improvement	169 (83.7)	53 (71.6)	
6MWT, m†			
Baseline	174 (110 to 255)	184 (118 to 286)	0.699
6 months	245 (179 to 333)‡	256 (165 to 340)§	0.948
Δ6MWT, months	59 (−4 to 119)	59 (−16 to 99)	0.525
Δ6MWT			
Worsening/no change	33 (27.5)	11 (30.6)	0.833
Improvement	87 (72.5)	25 (69.4)	
DASI‖			
Baseline	9.9 (7.2 to 15.5)	10.8 (7.2 to 15.7)	0.675
6 mo	17.9 (9.9 to 26.9)‡	15.5 (9.7 to 26.9)‡	0.284
ΔDASI			
Worsening/no change	40 (26.1)	17 (30.4)	0.609
Improvement	126 (73.3)	39 (69.6)	
ΔDASI	6.3 (0 to 11.8)	3.9 (−0.6 to 11.2)	0.293

Values are n (%) or median (25th to 75th, interquartile range). *Data available at baseline and at follow-up for 276 patients (no COPD, 202; COPD, 74). †Data available at baseline and at follow-up for 156 patients (no COPD, 120; COPD, 36). ‡$p < 0.0001$ vs. baseline. §$p = 0.01$ vs. baseline. ‖Data available at baseline and at follow-up for 228 patients (no COPD, 172; COPD, 56).
DASI = Duke Activity Status Index; other abbreviations as in Table 1.

increased mortality in COPD patients. The 4 factors of the BODE Index, BMI (B), degree of airflow obstruction (FEV_1) (O), dyspnea (D), and exercise capacity as evaluated by 6MWT (E) show an increased ability to predict mortality compared with FEV_1 alone. Puhan et al. (11) updated the BODE Index to include age as a prognostic factor for 3-year mortality in the primary care management of COPD and also demonstrated that the 6MWT was a much stronger predictor of mortality than BMI or FEV_1. Although the BODE Index cannot be directly extrapolated to the TAVI population, FEV_1, and 6MWT, 2 of the factors included in the BODE Index, were found to be predictors of clinical outcomes in COPD patients undergoing TAVI in this study.

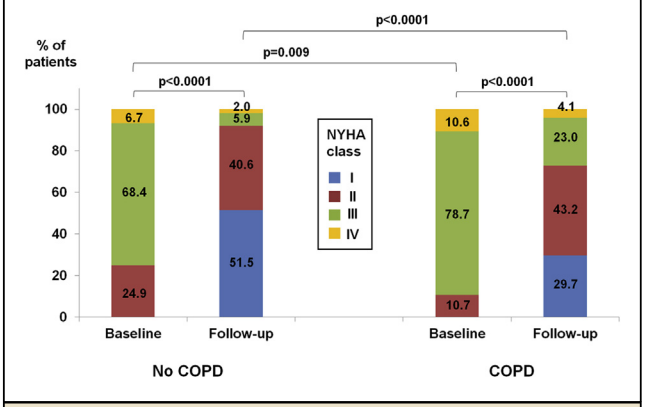

Figure 4. Changes in NYHA Functional Class Over Time

NYHA functional class changes after transcatheter aortic valve implantation according to the presence of COPD. Patients who died within the 6 months after transcatheter aortic valve implantation (n = 43) were not included in this analysis. COPD = chronic pulmonary obstructive disease; NYHA = New York Heart Association.

The 6MWT has been used in a variety of clinical studies to predict mortality. The SOLVD (Studies of Left Ventricular Dysfunction) Trial investigators (20) showed a higher mortality with a walked distance <300 m, whereas a distance of <200 m predicted surgical mortality in patients with COPD undergoing bilateral lung volume reduction surgery (21). In the TOPAS (True or Pseudo Severe Aortic Stenosis) study, a distance <320 m was a powerful predictor of reduced survival in patients with low-flow, low-gradient aortic stenosis (22). Recently it was shown that in SAVR, mortality at 12 months was associated with shorter preoperative 6MWT distances (23), and a cutoff distance of 300 m contributed to the risk stratification of patients undergoing SAVR. Our study demonstrated an inverse correlation of 6MWT distance with mortality and with treatment futility in COPD-TAVI patients. A baseline distance <150 m and <170 m best determined a higher risk of mortality and treatment futility, respectively. The significantly shorter cutoff distance in our patients highlights the fact that TAVI patients are more functionally impaired than patients with other life-threatening conditions. Importantly, the majority (two-thirds) of COPD patients who were not able to walk at least 170 m before the TAVI procedure either died or did not improve their NYHA functional class at follow-up. These findings suggest that in COPD patients, the 6MWT may represent 1 baseline test that will ultimately contribute to a TAVI risk index.

Pulmonary complications after surgical interventions are a major attributable factor of morbidity, mortality, prolonged hospital length of stay, and health care costs (24,25). Established risk factors for post-operative pulmonary complications have been well described and can be divided into patient- and procedure-related factors (26). Procedure-related factors include the use of general anesthesia, vascular surgery, thoracic surgery, emergency surgery, and prolonged procedures. All the TAVI procedures in our study were performed with patients under general anesthesia; hence, we are unable to draw any conclusions regarding general anesthesia as a contributory risk factor. TF-TAVI can, however, be performed with patients under local/regional anesthesia (27), and the potential advantages of this approach versus general anesthesia in patients with COPD merit further evaluation. With regard to patient-related factors for pulmonary complications, COPD has been shown to be an important predictor of post-operative pulmonary complications (28).

Table 5. Predictors of Periprocedural (30-day) Pulmonary Complications (n = 26) After TAVI in COPD Patients (n = 94)

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Baseline variables				
Age, yrs*	1.05 (0.99–1.12)	0.123		
Male	3.40 (1.15–10.10)	0.027	2.12 (0.56–8.04)	0.268
BMI, kg/m^2†	1.07 (0.98–1.17)	0.129		
NYHA functional class	—	0.963		
Smoker	0.97 (0.60–1.58)	0.908		
Diabetes	1.95 (0.78–4.87)	0.154		
Hypertension	1.16 (0.22–6.16)	0.861		
CAD	0.74 (0.30–1.87)	0.530		
Previous MI	0.63 (0.23–1.72)	0.370		
Previous AF	0.55 (0.20–1.56)	0.259		
Previous CABG	1.39 (0.56–3.45)	0.485		
Previous stroke	—	0.983		
Peripheral vascular disease	1.45 (0.58–3.60)	0.428		
eGFR <60 ml/min	0.91 (0.37–2.25)	0.837		
Frailty	1.59 (0.42–5.94)	0.495		
Porcelain aorta or severely calcified aorta	0.22 (0.05–1.24)	0.112		
DASI, %†	0.95 (0.88–1.03)	0.182		
6MWT, m‡	1.02 (0.94–1.11)	0.596		
FEV_1§	1.19 (1.03–1.38)	0.018	1.18 (1.02–1.38)	0.040
Pulmonary treatment				
Bronchodilators, >2	1.79 (0.71–4.51)	0.216		
Home oxygen	5.65 (1.23–25.95)	0.026	6.01 (0.95–37.87)	0.056
Glucocorticosteroids	1.93 (0.49–7.59)	0.346		
Echocardiographic variables				
Mean aortic gradient, mm Hg*	1.03 (0.99–1.06)	0.203		
Aortic valve area index, cm^2/m^2†	1.51 (0.24–9.67)	0.663		
LVEF, %*	1.02 (0.99–1.05)	0.286		
SPAP, mm Hg*	1.02 (0.98–1.06)	0.295		
Procedural characteristics				
Approach TA/Tao	2.54 (0.84–7.63)	0.100		
Procedural success	0.53 (0.14–2.04)	0.355		

*For each increase by 1 unit. †For each decrease by 1 log-transformed unit. ‡For each decrease in 6MWT by 20 m (data from 88 patients). §For each decrease of FEV_1 by 5%.

FEV_1 = forced expiratory volume in the first second of expiration; TAVI = transcatheter aortic valve implantation; other abbreviations as in Tables 1 and 2.

In more than one-fourth of our study's COPD-TAVI patients periprocedural pulmonary complications developed compared with <5% of non-COPD patients. Furthermore, approximately one-half of our study population were TA/TAo-TAVI, resulting in our overall 11.4% overall pulmonary complication rate (27.7% in COPD patients) comparable to that found in a recent study on thoracotomy in octogenarians (23.5%) (29). Although we could not identify TA/TAo-TAVI as a contributing factor, TF-TAVI, which does not alter thoracic wall mechanics, tended to be associated with a lower rate of pulmonary complications in COPD-TAVI patients. Importantly, a moderate degree of airway obstruction correlated with pulmonary complications in COPD-TAVI patients. The inverse correlation between FEV_1 and pulmonary complications emphasizes the potential role for optimization of pulmonary function, as with cardiac and general surgical procedures (29), before TAVI. In accordance with previous surgical studies (24,25), the occurrence of pulmonary complications was associated with a higher mortality rate at 30 days.

Study limitations. COPD in this study was defined according to STS criteria and not the GOLD (Global initiative for chronic Obstructive Lung Disease) definition. Although less used in respiratory medicine, the STS definition has been widely used in cardiac surgery, TAVI, and coronary intervention studies (1–4,30). A significant number of

Table 6. Univariate and Multivariate Predictors of Cumulative Overall Mortality (n = 37) in Patients With COPD (n = 94)

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Baseline variables				
Age, yrs*	1.05 (0.99–1.09)	0.050		
Male	1.67 (0.84–3.31)	0.143		
BMI, kg/m^2†	1.01 (0.94–1.08)	0.670		
NYHA functional class	—	0.989		
Smoker	0.98 (0.71–1.42)	0.981		
Diabetes	0.93 (0.49–1.78)	0.826		
Hypertension	0.70 (0.21–2.32)	0.561		
CAD	1.05 (0.54–2.06)	0.884		
Previous MI	1.15 (0.59–2.22)	0.672		
Previous AF	1.14 (0.56–2.31)	0.728		
Previous CABG	0.57 (0.28–1.15)	0.114		
Previous stroke	1.24 (0.17–9.15)	0.832		
Peripheral vascular disease	1.07 (0.54–2.13)	0.838		
eGFR <60 ml/min	2.04 (1.05–3.98)	0.036	1.87 (0.91–3.84)	0.089
Frailty	0.57 (0.14–2.37)	0.436		
Porcelain aorta or severely calcified aorta	0.17 (0.04–1.73)	0.096		
6MWT, m‡	1.17 (1.07–1.28)	0.009	1.16 (1.06–1.27)	0.013
FEV_1‡	1.02 (0.92–1.15)	0.636		
Pulmonary treatment				
Bronchodilators, >2	1.30 (0.57–3.01)	0.533		
Home oxygen	1.06 (0.41–2.79)	0.899		
Glucocorticosteroids	1.43 (0.53–3.72)	0.458		
Echocardiographic variables				
Mean aortic gradient, mm Hg*	0.97 (0.94–0.99)	0.028	0.98 (0.95–1.01)	0.109
Aortic valve area index, cm^2/m^2†	1.72 (0.32–9.10)	0.526		
LVEF, %*	1.00 (0.98–1.02)	0.983		
SPAP, mm Hg*	1.01 (0.99–1.04)	0.334		
Procedural characteristics				
Approach TA/TAo	1.13 (0.51–2.51)	0.769		
Procedural success	1.37 (0.60–3.12)	0.461		

*For each increase by 1 unit. †For each decrease by 1 log-transformed unit. ‡For each decrease in 6MWT by 20 m (data from 88 patients). Abbreviations as in Tables 1, 2, and 5.

potential candidates for TAVI were unable to perform the 6MWT either at baseline or follow-up, mostly because of poor mobility or logistic reasons, and this might have introduced some bias in the final results. However, baseline 6MWT was performed in most patients (82%), and close to 90% of surviving patients who had baseline 6MWT repeated the test at follow-up, which allowed us an accurate estimation of change in exercise capacity. The relatively low number of fatal events at 30 days precluded performance of a multivariate analysis to determine the prognostic role of COPD on 30-day mortality. All TAVI procedures were performed under general anesthesia and transesophageal echocardiography guidance, and more than half of the patients underwent the procedure by TA/TAo approach. These results might therefore not apply to TAVI procedures performed with local anesthesia and without thoracotomy, and future studies will have to evaluate the impact of COPD on patients undergoing this type of TAVI procedures. Finally, the COPD cohort included a relatively small number of patients, and the results regarding the prognostic factors in COPD patients will have to be confirmed in larger studies. Also, larger studies will be needed to evaluate the predictive factors of periprocedural complications (multivariate model slightly overfitted) and the prognostic value of oxygen dependency or steroid therapy among COPD patients.

Table 7. Main Baseline and Procedural Variables in COPD Patients According to the Occurrence of Treatment Futility (Death or No Improvement in NYHA Functional Class at 6-Month Follow-up)

	Treatment Futility			
	No (n = 54)	Yes (n = 40)	OR (95% CI)	p Value
Baseline variables				
Age, yrs*	78 ± 8	79 ± 8	1.01 (0.96–1.06)	0.743
Male	32 (59.3)	26 (65.0)	1.22 (0.52–2.86)	0.649
BMI, kg/m^2†	28 ± 6	27 ± 5	0.98 (0.91–1.06)	0.647
Smoker	6 (11.1)	2 (5.0)	0.84 (0.54–1.31)	0.436
Diabetes	26 (48.2)	17 (42.5)	0.80 (0.35–1.81)	0.587
Hypertension	50 (92.6)	36 (90.0)	0.72 (0.17–3.07)	0.657
CAD	35 (64.8)	24 (60.0)	0.81 (0.35–1.89)	0.633
Previous MI	17 (31.5)	15 (37.5)	1.31 (0.55–3.09)	0.543
Previous AF	18 (33.3)	12 (30.0)	0.86 (0.36–2.07)	0.732
Previous CABG	24 (44.4)	14 (35.0)	0.67 (0.29–1.56)	0.357
Previous stroke	0	2 (5.0)	999 (0.01–999)	0.979
Peripheral vascular disease	28 (51.9)	20 (50.0)	0.93 (0.41–2.10)	0.859
eGFR <60 ml/min	21 (38.9)	24 (60.0)	2.35 (1.02–5.44)	0.045
STS-PROM score*	8.0 ± 4.6	9.2 ± 5.0	1.05 (0.97–1.15)	0.240
Frailty	6 (11.1)	5 (12.5)	1.14 (0.32–4.05)	0.836
Porcelain aorta or severely calcified aorta	14 (25.9)	7 (17.5)	0.61 (0.22–1.68)	0.335
DASI, %†	10.8 (7.2–17.9)	8.6 (7.2–14.9)	1.07 (0.99–1.14)	0.067
6MWT, m‡	188 (118–316)	100 (33–206)	1.16 (1.02–1.19)	0.011
FEV_1§	60.6 ± 20.3	59.0 ± 22.6	1.00 (0.97–1.02)	0.749
Pulmonary treatment				
Bronchodilators, >2	36 (66.7)	27 (67.5)	1.50 (0.53–4.22)	0.443
Home oxygen	3 (5.6)	5 (12.5)	2.58 (0.58–11.58)	0.216
Glucocorticosteroids	4 (7.4)	6 (15.0)	2.42 (0.64–9.50)	0.190
Echocardiographic variables				
Mean aortic gradient, mm Hg*	39.8 ± 12.3	34.9 ± 12.1	0.97 (0.93–1.00)	0.068
Aortic valve area index, cm^2/m^2†	0.27 ± 0.06	0.26 ± 0.07	1.88 (0.35–10.1)	0.463
LVEF, %*	53.7 ± 14.2	53.1 ± 15.1	0.99 (0.97–1.03)	0.838
SPAP, mm Hg*	46.8 ± 12.8	47.0 ± 14.6	1.00 (0.97–1.04)	0.952
Procedural characteristics				
Approach TA/TAo	33 (61.1)	25 (62.5)	1.38 (0.56–3.39)	0.486
Procedural success	42 (77.8)	28 (70.0)	1.31 (0.43–4.03)	0.635

Values are mean ± SD, median (interquartile range), or n (%). *For each increase by 1 unit. †For each decrease by 1 log-transformed unit. ‡For each decrease in 6MWT by 20 m (data from 88 patients). §For each decrease of FEV_1 by 5%.

Abbreviations as in Tables 1, 2, and 4.

Conclusions

In patients with severe symptomatic aortic stenosis undergoing TAVI, comorbid COPD is a major risk factor for mortality at 1-year follow-up, driven by higher rates of death from respiratory causes. A lower exercise capacity before the intervention is an important predictor of mortality and treatment futility among COPD patients, whereas a higher degree of airway obstruction predicts periprocedural pulmonary complications. These results highlight the importance of a global pre-procedural functional and respiratory assessment in COPD-TAVI patients as it may help predict prognosis and patient selection. Future studies will have to determine the potential usefulness of measures to optimize pulmonary function pre- and post-TAVI to improve clinical outcomes in patients with COPD.

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